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(54) MELTRINS

MELTRINE

MELTRINES

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Description

Technical Field

[0001] This invention relates to Meltrins and polypeptides of the respective domains thereof; DNAs encoding the same; antisense oligonucleotides for these DNAs; various antibodies against these Meltrins and the polypeptides of the respective domains thereof; expression vectors comprising the DNAs; transformants constructed by using these expression vectors; a process for producing the above-mentioned meltirins and the polypeptides of the respective domains thereof by means of the transformants; and medical compositions comprising the Meltrins or Meltrin antagonists as an effective ingredient.

Background Art

[0002] In the course of myotube formation, myoblasts, which have divided from myogenic cells originating in undifferentiated mesodermal cells and grown to differentiate, will start synthesizing muscle-specific substances such as myosin and actin after its final division, and will lose cell boundaries at the fusion surface to be tansformed into multinucleate syncytium named myotube through adhesion and fusion of cytoplasmic membranes with neighbouring cells of the same kind.

[0003] There have been already reported several kinds of membrane proteins involved in the myotube formation, such as N-Cadherin (Knudsen, K.A. et al., Expl. Cell Res., 188, 175-184 (1990), Merge, R.M. et al., J. Cell Sci., 103, 897-906 (1992)), M-Cadherin (Donalies, M. et al., Proc. Natl. Acad. Sci., U.S.A. 88, 8024-8028 (1991)), N-CAMs (Merge, R.M. et al., J. Cell Sci., 103, 897-906 (1992) and others), V-CAMs and Integrins (Rosen, G.D. et al., Cell 69, 1107-1119 (1992) and others).

[0004] However, the molecular mechanism has not yet been sufficiently understood concerning the course of formation of the multinucleate syncytium named myotube through adhesion and fusion of the cytoplasmic membranes of the myoblasts with each other.

[0005] On the other hand, the substances named "fusion peptides" have been known as an adhesion factor involved in the course of infectior of cells with viruses (Morrison, T.G. Virus Res., 10, 113-136 (1988) and the others). Fertilin, which was recently isolated as a factor involved in sperm-egg adhesion, has been found to contain a sequence similar to the fusion peptide of rubella virus (Biobel, C.P. et al., Nature 356, 248-252 (1992) and the others).

[0006] Many substances having adhesion activity are known as mentioned above, and substances which may inhibit the activity of Integrins and the like have been developed and studied as potential medical agents.

[0007] The present inventors have now isolated novel substances involved in adhesion. Particularly, on the assumption that some fusion peptide-like adhesion factor like in sperm-egg adhesion may be involved in adhesion and fusion of the myoblasts with each other in the course of myotube formation, the novel substances involved in cell adhesion have been cloned and named "Meltrins", by using highly conserved sequences in Fertilin α and β as a probe.

Disclosure of Invention

[0008] The present invention relates to a novel "Meltrin." "Meltrins" are characterized as proteins which are expressed in the course of differentiation-induction of muscle cells and to contain the highly conserved sequences in Fertilin α and β. Meltrins are also characterized as proteins which are involved in fusion, adhesion,or aggregation of cells. Thus, some kinds of cells such as muscle ones may fuse, aggregate or adhere via Meltrins.

[0009] Cell fusion means that more than two cells fuse with each other to form one multicleate syncytium. Adhesion of cells means that more than two cells adhere to each other. Aggregation of cells means that more than two cells (particularly the cells present in liquid) flock together to form a mass of cells. It may be considered that cells adhere to each other, followed by cell fusion and aggregation.

[0010] According to the invention, there is thus provided a soluble meltrin polypeptide which does not comprise a transmembrane domain or an intracellular domain and which comprises the amino acid sequence of Gly (No.1) to Ile (No. 686) from the N-terminal in Fig. 15a - Fig. 15f, or the amino acid sequence of Glu (No. 156) to Ile (No. 686) from the N-terminal in Fig.15a - Fig.15f.

[0011] The invention also provides:

- a DNA comprising a base sequence encoding the polypeptide of the invention;
- a DNA of the invention which comprises the base sequence of No.1 to No. 2058 from the 5' terminal in Fig. 15a - Fig. 15f;
- a DNA of the invention which comprises the base sequence of No. 1 to No. 2848 from the 5' terminal in Fig. 15a - Fig. 15f;

- an antisense oligonucleotide which hybridizes with a part of the sequence of No. 1957 to No. 2848 from the 5' terminal in Fig. 15a - Fig. 15f;
- an antibody which recognizes the C-terminal region of a meltrin wherein the C-terminal region is from amino acid No. 653 to No. 686 from the amino terminal in Fig. 15a - Fig. 15f;
- a vector comprising a DNA of the invention;
- a transformant by the vector of the invention;
- a process for producing a polypeptide of the invention, which process comprises culturing the appropriate transformant of the invention;
- a medical composition comprising a polypeptide, an antisense oligonucleotide or an antibody of the invention;
- use of a polypeptide, an antisense oligonucleotide or an antibody of the invention for the manufacture of a medicament for treatment of a condition associated with unhealthy enhanced bone resorption; and
- use of a polypeptide, an antisense oligonucleotide or an antibody of the invention for the manufacture of a medicament for preventing metastasis of cancer cells.

At least three kinds of molecules (α, β and γ) have been isolated from one animal species.

[0012] Meltrins may be mouse Meltrins α ,β and γ, which are characterized by amino acid sequences shown in Fig. 2a - Fig.2j, Fig.3a - Fig.3j and Fig.4a - Fig.4i, respectively, or partial sequences thereof.

[0013] Other examples are human Meltrins α, β and γ, which are characterized by amino acid sequences shown in any one of Fig.12a - Fig.12b, Fig.15a - Fig.15f or Fig.23a - Fig.23b; any one of Fig.16 or Fig.17a - Fig.17c; or Fig.13a - Fig.13d, respectively, or partial sequences thereof.

[0014] The above amino acid sequences should be considered only examples of Meltrins. Any variant of the above amino acid sequences wherein a part of the sequences has changed due to deletion, substitution, addition, insertion and the like of amino acids is therefore a Meltrin, as long as it is expressed in muscle cells, and have the highly conserved sequences in Fertilin α and β or is involved in fusion, adhesion or aggregation of cells. As shown now by the present inventors, a high homology is seen in the part from disintegrin domain to cysteine-rich region of mouse amino acid sequences shown in Fig.2a - Fig.2j and human amino acid sequences shown in Fig.12a - Fig.12b. It is considered that such substances as showing homology of about 80 % or more, preferably about 90 % or more to the above amino acid sequences may keep the function as Meltrin. Particularly, it is believed that the substances having the sequences with homology of about 80 % or more, preferably about 90 % or more to the region from metalloproteinase domain to disintegrin domain of mouse or human Meltrins α, β and γ will have substantially the same activity, even if all of the other sequences are different from them. Accordingly, Meltrins may include substances having a high homology to the above amino acid sequences or to a part thereof and showing substantially the same activity as mouse or human Meltrins.

[0015] In other words, Meltrins may be characterized by having amino acid sequences encoded by base sequences that may hybridize the sequences complementary to the base sequences encoding any one of the amino acids shown in Fig.2a - Fig.2j, Fig.3a - Fig.3j, Fig.4a - Fig.4i, Fig.12a - Fig.12b, Fig.13a - Fig.13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c or Fig.23a - Fig.23b.

[0016] Meltrins exist in bodies as a membrane protein consisting of intracellular domain, transmembrane domain, and extracellular domain; and as a soluble protein having no transmembrane domain. The extracellular domain contains precursor domain, metalloproteinase domain, disintegrin domain, and cysteine-rich region. Meltrin α has a fusion peptide-like sequence in its cysteine-rich region (Refer to Fig.8).

[0017] The disintegrin domain is indispensable for the function of Meltrins such as adhesion, fusion and aggregation of cells. On the other hand, the precursor and metalloproteinase domains are thought to be regulating sequences for Meltrins to show the activity in a specific organ or tissue, or under specific conditions. It is known that the disintegrin found in snake venom will adhere to platelet IIb/IIIa. It is therefore presumed that the disintegrin domain by itself may have the function to adhere to cells. The metalloproteinase domain may act by itself as a protease as such.

[0018] A polypeptide may comprise any part of a Meltrin. Such polypeptides include the respective domain per se of Meltrins, polypeptides comprising at least the respective domain of Meltrins, any part of the sequences of Meltrins, polypeptides comprising at least any part of the sequences of Meltrins, and polypeptides comprising at least the sequence having the combination of any of the respective domains of Meltrins and any part of Meltrins in any order.

[0019] The above polypeptides which are chemically modified or formed into salts thereof.

[0020] The preferable examples of the such polypeptides include polypeptides consisting of a part of the disintegrin domain, polypeptides consisting of the disintegrin domain per se, polypeptides comprising at least the disintegrin domain, polypeprides comprising at least the disintegrin and cysteine-rich regions, polypeprides comprising at least the metalloproteinase, disintegrin and cysteine-rich regions, polypeptides consisting of a part of the metalloproteinase domain, and polypeptides consisting of the metalloproteinase domain per se.

[0021] There may be mentioned as other preferable examples of the present polypeptides those comprising at least the disintegrin and cysteine-rich regions, but not comprising the transmembrane domain, or comprising neither the transmembrane domain nor intracellular domain; and those comprising at least the metalloproteinase, disintegrin and

cysteine-rich regions, but not comprising the transmembrane domain, or comprising neither the transmembrane domain nor intracellular domain. Such polypeptides comprising no transmembrane domain are a soluble one which will be secreted through a cell membrane into extracellular area. The soluble polypeptides may be collected from supernatant of the culture medium of cells. When optionally combined downstream of a suitable signal sequence and expressed by cells in a genetic engineering process, it will be secreted into the culture supernatant and advantageously collected therefrom with a high efficiency.

[0022] The amino acid sequences in Fig.2a - Fig.2j, Fig.3a - Fig.3j, Fig.4a - Fig.4i, Fig.12a - Fig. 12b, Fig.13a - Fig. 13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c and Fig.23a - Fig.23b, which correspond to the precursor domain, metalloproteinase domain, disintegrin domain, cysteine-rich region, intracellular domain, and transmembrane domain of mouse and human Meltrins α , β and γ, are discussed in the Examples. It should be noted, however, that the polypeptides having the above corresponding amino acid sequences constitute only examples. That is to say, polypeptides essentially comprising the same amino acid sequences may also be prepared. Thus, the boundaries of each domain are not limited to those defined in the Examples. Polypeptides comprising the domains wherein the boundaries are shifted to N-, C-terminals or both by 1 to about 20 amino acids from the boundaries defined in the Examples may also be prepared, as long as they have substantially the same function as that of the above polypeptides. Similarly, the polypeptides wherein a part of the amino acid sequences has changed due to deletion, substitution, addition, insertion and the like of amino acids may also be prepared, as long as they have substantially the same function as that of each domain.

[0023] It is considered that the polypeptides comprising such amino acid sequences as showing homology of about 80 % or more, preferably about 90 % or more to the amino acid sequences in each domain of the above figures may have the same function as that of the polypeptide of the present invention.

[0024] The Meltrin of the present invention may be used to bond cells to each other or to apparatuses such as a plate. It may be also fused with any other substances to efficiently deliver the substances to muscle cells upon its application into culture systems of the muscle sells, tissues or bodies.

[0025] On the other hand, the polypeptides comprising at least a part of Meltrins may be added to the culture systems to competitively inhibit the adhesion, fusion or aggregation of cells. Particularly, the disintegrin domain per se, a part thereof, or a soluble polypeptide comprising the disintegrin domain may be used as an effective ingredient in a medical composition for inhibiting the adhesion of cells. For example, such medical composition may be used as an anticoagulant to inhibit thrombus formation or blood coagulation, and be used to treat thrombosis, DIC and multi-organ failure. Furthermore, since it is considered that adhesion factors such as integrin family are involved in metastasis of cancer cells, the polypeptides comprising the disintegrin domain may be used as a drug for inhibiting the growth of cancers, or the adhesion of cancer cells to other cells so as to prevent their metastasis. In addition to the above, it is known that the adhesion of cells plays an important role in formation of osteoclast. The examples will demonstrate that Meltrins are involved in the adhesion in the formation of osteoclast, and anti-Meltrin antibodies may inhibit the formation of osteoclast and the increase of bone resorption. Accordingly, the polypeptide of the present invention may be used as an effective ingredient in a medical composition for inhibiting the increase of bone resorption, like as anti-Meltrin antibodies,

[0026] Among the polypeptides comprising at least a part of the Meltrin of the present invention, those comprising the metalloproteinase domain may act as a protease by itself, or be used to competitively inhibit the activity of other proteases so that they may be utilized as a drug for treating inflammatory diseases.

[0027] The Meltrin polypeptide of the present invention may also be used as an antigen for producing antibodies.

[0028] The present invention also relates to DNAs comprising the base sequence encoding the amino acid sequences of the Meltrin of the present invention or the polypeptides comprising any parts thereof.

[0029] The above DNAs include any type of DNAs such as genomic DNAs and cDNAs.

[0030] Examples of DNAs encoding Meltrins are those encoding mouse Meltrins α, β, and γ, or the polypeptides comprising any parts thereof, which are characterized by the coding regions shown as the base sequences in Fig.5a - Fig.5j, Fig.6a - Fig.6h, and Fig.7a - Fig.7e, respectively, or partial sequences thereof. Other examples are those encoding human Meltims α, β, and γ, or the polypeptides comprising any parts thereof, which are characterized by the coding regions of the sequences shown as the base sequences in any one of Fig.12a - Fig.12b, Fig. 15a - Fig. 15f or Fig.23a - Fig.23b; any one of Fig.16 or Fig.17a - Fig.17c; or Fig.13a - Fig.13d, respectively, or partial sequences thereof.

[0031] The base sequences in the above figures, which correspond to the precursor domain, metalloproteinase domain, disintegrin domain, cystein-rich domain, intracellular domain, and transmembrane domain of mouse and human Meltrins α ,β and γ, are discussed in the Examples. It should be noted, however, that they constitute only examples of such DNAs. DNAs essentially comprising the same base sequences may also be prepared.

[0032] Thus, the boundaries of each domain are not limited to those defined in the Examples. And the DNAs comprising sequences encoding the domains wherein the boundaries are shifted to 5'-, and/or 3'-ends by 1 to about 60 base pairs from the boundaries defined in the Examples may also be prepared, as long as they encode the polypeptides having substantially the same function as that of each domain.

[0033] In addition of the above base sequences, DNAs may be prepared comprising the base sequences or partial sequences thereof, which encode the same amino acid sequences as above prepared by means of chemical synthesis

or genetic engineering in consideration of degeneracy of codons. As now shown by the present inventors, a high homology is seen in mouse and human Meltrins. It is therefore considered that the substances showing homology of about 80 % or more, preferably about 90 % or more to the above amino acid sequences may keep the function as Meltrin, and that DNAs encoding such homologous polypeptides will hybridize with each other. Accordingly, DNA fragments may be obtained by hybridization under stringent conditions using the DNAs having the base sequences complementary to those in the above figures as a probe.

[0034] The DNAs of mouse or human Meltrins α, β and γ, or partial sequences thereof may be inserted into plasmid vectors. Strains of E. coli transformed by the same plasmid vectors have been deposited with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology.

[0035] The DNAs described herein may be prepared by known methods. The cDNAs, for example, may be prepared by using cDNA library and known PCR (e.g., Michael A.I. et al., PCR Protocols, a guide to method and application, Academic Press, 1990) with degenerative primers for a part of the amino acid sequences (for example, the degenerative primer encoding the amino acid sequences of the disintegrin domain) shown in Fig.2a - Fig.2j, Fig.3a - Fig.3j, Fig.4a - Fig.4i, Fig.12a - Fig. 12b, Fig.13a - Fig.13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c and Fig.23a - Fig.23b. The DNAs described herein may also be prepared by hybridization method using a probe prapared on the basis of the base sequences of the above amplified DNA fragments.

[0036] As demonstrated in the Examples, the preferable source of cDNA library include cells obtained by inducing myoblast to differentiate, bone marrow and fetal pulmonary cells. Known cDNA libraries prepared from placenta, chorionic cells and fetal cells may also serve as the source of cDNA library in the present invention.

[0037] Among the DNAs described herein, one encoding the polypeptide in which any parts of Meltrins are combined in any order may be prepared by the following steps. That is, each DNA fragment encoding any part of Meltrins is amplified by PCR, in which the primers may be optionally modified in order to provide an appropriate restriction enzyme site. The amplified DNA fragments are ligated with each other by DNA ligase, so that a reading frame should not be shifted.

[0038] The DNAs described herein may be used for producing the Meltrins or polypeptides of the present invention by means of genetic engineering. Such prodution may be carried out with reference to known methods (for example, Sambrook J. et al., Molecular Cloning a Laboratory Manual 2nd ed., Cold Spring Harbor Laboratory, New York, 1989).

[0039] The DNAs described herein inserted into suitable vectors may also be used in gene therapy. The base sequence encoding any physiologically active substances is fused downstream of the present DNAs followed by insertion of the resulting fused DNA into a vector originated in an appropriate virus, and cells in a living body are transformed with the resulting vector, so that the physiologically active substances may be expressed as a fused protein with the Meltrin of the present invention. The thus expressed physiologically active substances will be delievered near to the cells to which Meltrins adhere.

[0040] The present invention further relates to antisense oligonucleotides and derivatives thereof for the DNAs encoding the Meltrin of the present invention or for the polypeptides comprising any part thereof.

[0041] The present antisense oligonucleotides and derivatives thereof are characterized by their base sequences complementary to those encoding Meltrins or a part thereof, or by their function to inhibit the expression of Meltrins or the polypeptides comprising any part thereof. The antisense oligonucleotides and derivatives thereof characterized by the latter feature include those complementarily bonding to the non-coding regions existing upstream or downstream of the coding regions of Meltrins as well as those complementarily bonding to the coding regions of Meltrins or any part thereof.

[0042] Examples of the antisense oligonucleotides and derivatives thereof described herein include the base sequences complementary to the DNAs of the present invention or any part thereof, particularly to those shown in Fig. 5a - Fig. 5j, Fig.6a - Fig.6h, Fig.7a - Fig.7e, Fig.12a - Fig.12b, Fig.13a - Fig.13d, Fig. 15a - Fig. 15f, Fig.16, Fig.17a - Fig.17c and Fig.23a - Fig.23b. Uracil (U) may be used instead of thymine (T) as a complementary base to adenine (A).

[0043] The derivatives of the present antisense oligonucleotides include any one that is similar to the antisense oligonucleotides in steric structure and function, such as those wherein other substances are bound to 3'- or 5'-end of the oligonucleotides; those wherein at least one of bases, sugars or phosphoric acids in the oligonucleotides has substitution or modification; those having non-naturally occurring bases, sugars or phosphoric acids; and those having back bone other than that of sugars-phosphoric acids.

[0044] The antisense oligonucleotide of the invention and derivatives thereof may be prepared by known methods (for example, ed., Stanley T. Crooke and Bernald Lebleu, in Antisense Research and Applications, CRC Publishing, Florida, 1993).

[0045] The present antisense oligonucleotide of a naturally occurring type may be prepared by chemically synthesizing sense-primers and antisense-primsers having the base sequences complementary to 3'- or 5'-end of the antisense oligonucleotide sequences, followed by PCR using the Meltrin genes or RNAs encoding Meltrins as a template. Otherwise, the derivatives of the antisense oligonucleotides such as a methylphosphonate and phosphorothionate types may be prepared by means of a chemical synthesizer (e.g., Perkin Elmer Japan Co., Type 394) accoding to the manual attached to the chemical synthesizer, followed by, if necessary, purification of the synthesized products in HPLC method using

reversed phase chromatography and the like.

[0046] The present antisense oligonucleotide and derivatives thereof may be labelled with radioisotopes, fluorescent substances, enzymes or luminescent substances and used as a probe for detecting the existence of Meltrins or any part thereof in a sample. The present antisense oligonucleotide may also be used as a medical composition for inhibiting the expression of Meltrins in a living body.

[0047] For the purpose of inhibiting the expression of Meltrins by using the present antisense oligonucleotide and derivatives, they may be solubilized or suspended in a suitable solvent, enclosed in a liposome, or inserted into a suitable vector.

[0048] It is preferred that the present antisense oligonucleotide and derivatives thereof used in the medical composition should have a pharmaceutically acceptable purity and be used in a pharmaceutically acceptable way.

[0049] As already mentioned in the above, it is considered that Meltrins are involved in formation of osteoclast, growth and metastasis of cancers as well as skeletal myogenesis. Accordingly, the present antisense oligonucleotide and their derivatives which are capable of inhibiting the expression of Meltrins may be used in in the manufacture of a medicament treatment and prevention of cancers, treatment of osteoporosis and hypercalcemia by inhibiting bone resorption.

[0050] The present invention also relates to antibodies recognizing the Meltrin of the present invention or the polypeptides comprising at least any part thereof. In other words, they include those recognizing only Meltrins of the present invention, those recognizing only the polypeptides of the present invention and those recognizing both of them.

[0051] Antibodies described herein include those cross reacting with other polypeptides in addition to those specifically recognizing Meltrins and the polypeptides of the present invention. They also include those specifically recognizing any one of Meltrins α, β and γ, and those specifically recognizing more than two of Meltrins α, β and γ, as well as those recognizing only Meltrins originated in a particular animal such as human and mouse or only the polypeptides comprising at least any part thereof, and those recognizing Meltrins originated in more than two kinds of animals or the polypeptides comprising at least any part thereof.

[0052] Such antibodies include those recognizing the amino acid sequences in Fig.2a - Fig.2j, Fig.3a - Fig.3j, Fig.4a - Fig.4i, Fig.12a - Fig.12b, Fig.13a - Fig.13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c or Fig.23a - Fig.23b, or any part thereof.

[0053] More preferably, the antibodies described herein are those obtained by immunization of animals with the polypeptides comprising said amino acid sequences or any part thereof as an antigen, which may be optionally conjugated with a suitable carrier.

[0054] Such antibodies may be prepared by inserting DNA comprising the base sequnces shown in Fig.5a - Fig.5j, Fig.6a - Fig.6h, Fig.7a - Fig.7e, Fig.12a - Fig.12b, Fig.13a - Fig.13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c or Fig. 23a - Fig.23b or any part thereof into a suitable expression vector, tranforming a suitable host cell by the vector to produce Meltrins, which are purified from cell bodies of the transformant or culture medium and administered as an antigen. The cell bodies per se of the transformant or any cells expressing Meltrins per se may be administered as an antigen. Such transformant or cells may express any one of Meltrins α, β and γ, or more than two kinds of them. The antibodies may be also prepared by chemically synthesizing the polypeptides having a part of the amino acid sequences of Meltrins, conjugating them with a carrier such as KLH (Keyhole Limpet Hemocyanin) and administering them as an antigen.

[0055] It is possible to prepare the present antibody that may recognize the whole of Meltrins even when the part of Meltrins is used as an antigen to be administered. It is also possible to prepare the present antibody that may recognize human Meltrins or any part thereof even when mouse Meltrins or any part thereof are used as an antigen to administered.

[0056] The antibodies described herein include monoclonal and polyclonal ones, and may belong to any class or subclass.

[0057] The antibodies may be prepared according to known methods (e.g., "Meneki jikkenho (Laboratory manual of Immunology)" published by Japan Immunological Society). An example of the known methods will be described below.

[0058] A suitable cell is transformed by an expression vector comprising the coding regions of the base sequences shown in Fig.5a - Fig.5j, Fig.6a - Fig.6h, Fig.7a - Fig.7e, Fig.12a - Fig.12b, Fig.13a - Fig.13d, Fig.15a - Fig.15f, Fig.16, Fig.17a - Fig.17c or Fig.23a - Fig.23b or any part thereof, and used as an antigen as such. Alternatively, Meltrins produced by the transformant are purified from cell bodies of the transformant or culture medium to be used as an antigen, or polypeptides consisting of amino acid sequences shown in the above figures are chemically synthesized, cojugated with a carrier such as KLH (Keyhole Limpet Hemocyanin) and purified to be used as an antigen.

[0059] Animals are inoculated with the antigen thus prepared, alone or together with a suitable adjuvant such as Freund's complete adjuvant (FCA) or Freund's incomplete adjuvant (FIA), subjected to boosting at two to four-week intervals. After boosting, the blood is drawn from the animals and antiserum is obtained therefrom. Animals to be immunized may be selected from rat, mouse, rabbit, sheep, horse, fowl, goat, pig, cattle and the like, depending on the kind of the antibody to be desired. Polyclonal antibodies may be obtained by purification of the antiserum by known methods such as salting-out, ion-exchange chromatography, affinity chromatography and any combination thereof.

[0060] Monoclonal antibodies may be prepared as follows. Antibody-producing cells such as spleen cells and lym-

phocytes are collected from the immunized animals, fused with myeloma and the like by known methods using polyethyleneglycol, Sendai virus, electrical pulse to give hybridomas. Clones which produce an antibody bonding to the Meltrin of the present invention are then selected and cultured. Monoclonal antibodies of the present invention are purified from the culture supernatant of the selected clones by known methods such as salting-out, ion-exchange chromatography, affinity chromatography and any combination thereof.

[0061] The present antibodies may be neutralizing antibodies, which inhibit the fusion, adhesion or aggregation of cells by Meltrins. The neutralizing antibodies of the present invention include those that can completely inhibit the activity of Meltrins, and those partially inhibit the same.

[0062] The neutralizing antibodies may be screened by adding antiserum or culture supernatant of the hybridomas to the culture system of Meltrin-expressing cells to evaluate the degree of inhibition of fusion or aggregation of cells. After the screening, the desired antibodies may be purified from the thus selected antiserum or culture supernatant of the hybridomas by the known methods.

[0063] The antibodies of the present invention include Fab, F(ab'), $F(ab')_2$ and Fv, as long as they recognize and bond to the present polypeptides or any part thereof. A single chain Fv may be also included in the present antibodies, which is obtained by constructing a gene encoding the single chain Fv wherein H and L chains are linked into a single chain and being expressed by a suitable host cell. Chimera antibodies, human antibodies and humanized antibodies are also included in the present invention, as long as they recognize and bond to the present polypeptides or any part thereof.

[0064] For example, the chimera antibodies may be prepared by substituting a gene encoding the constant region of human antibodies for a gene encoding the constant region of the mouse antibodies recognizing Meltrins or the polypeptides of the present invention, expressing the thus reconstituted gene in animal cells. The human antibodies may be prepared by, for example, in vitro sensitization method (Borrebaeck, C.A.K.J. Immunol., Meth., 123, 157, 1989) or the method using SCID mouse (Toshio KUDO, Tissue Culture, 19, 61-65, 1993). The humanized antibodies may be prepared by reconstituting a gene so that complementary determining regions (CDR) of the human antibodies are replaced with those of the mouse antibodies, and expressing the gene in animal cells (Carter et al., Pro. Nat. Acad. Sci, 89, 4285, 1992).

[0065] If necessary, amino acids in a framework of the variable region of the humanized antibodies thus reconstituted may be replaced, so that the framework should have a high homology to that of the mouse antibodies and CDR of said humanized antibodies may form an appropriate antigen-binding site. The preferred examples of the humanized antibodies are those having the same CDR as the neutralizing antibodies F932-15-2 and F937-9-2. For the preparation of these preferred humanized antibodies, the DNA encoding the antibodies is prepared from the hyridoma F932-15-2 or F937-9-2, and linked with the DNAs encoding human antibodies so that the sequences other than CDRs should originate in the human antibodies. Any variation may be optionally introduced into the DNA encoding the framework portion. The thus obtained DNA is then inserted into a suitable expression vector to transform a suitable cell, and the humanized antibodies are purified from the culture supernatant of the transformant.

[0066] The present antibodies may be labelled with fluorescent substances, enzymes, luminescent substances or radioisotopes to detect Meltrins or their decomposed products present in body fluid or tissues. Since it is considered that Meltrins are involved in formation of myotube, resorption of bone and metastasis of cancers as already mentioned in the above, the detection of the existence of Meltrins in body fluid or tissues would make it possible to estimate the progress of diseases and prognosis and to confirm the effects of treatments. The present antibodies may be also used to provide an antibody affinity column, or to detect Meltrins in a fraction during the course of purification of Meltrins.

[0067] The neutralizing antibodies of the present invention may serve as an effective ingredient of a medical composition for inhibiting bone resorption, inflammatory diseases, blood coagulation and metastasis of cancers, owing to their ability to inhibit fusion or adhesion of cells. They may serve as an agent used in culture to inhibit the aggregation of cultured cells. When used as the effective ingredient of the medical composition, the human or humanized antibodies are preferred from the viewpoint of their antigenicity.

[0068] Also, the present invention relates to a vector comprising the DNA of the present invention. The present vector may further contain, if necessary, an enhancer sequence, promoter sequence, ribosome-binding sequence, base sequence for amplification of the number of copies, sequence encoding signal peptides, sequences encoding other polypeptides, poly(A)-additional sequence, splicing sequence, origin of replication, base sequence of the gene for selective markers and so on.

[0069] The present vector may be prepared by inserting the DNAs of the present invention into any vectors according to known methods (e.g., Molecular Cloning, a Laboratory Manual 2nd ed., Cold Spring Harbor Laboratory, New York, 1989). The preferable examples of the DNAs encoding Meltrins or any part thereof have been already disclosed in the present specification. The present vectors include a plasmid vector, phage vector and virus vector; pUC118, pBR322, pSV2-dhfr, pBluescriptII, PHIL-S1, λZap II, λgt10, pAc700, YRP17, pEF-BOS and pEFN-II being preferred.

[0070] The preferred vectors of the present invention may optionally comprise the origin of replication, selective markers, and promoter in addition to the DNAs encoding Meltrins or the polypeptides comprising at least any part thereof so as to be used to express Meltrins or the same polypeptides. As the origin of replication, ColEI, R factor, F factor and so on may be used in the vectors for E.coli; SV40- or adenovirus-derived ones in the vectors for animal cells; and ARS1-

derived one in the vectors for yeast. As the promoter, trp, lac and tac promoters may be used in the vectors for E. coli; SV40-, cytomegalovirus-, and adenovirus-derived ones, and those intrinsically existing in the genes of human or animals such as the promoter region of an elongation factor 1α in the vectors for animal cells; and α promoter in the vectors for yeast, especially AOX1 promoter in the case of Pichia yeast. In the addition to the above sequences, the present vectors may further comprise, if necessary, RNA splicing site, signal for poly-adenylation and the like for the transforamtion of eucaryotic cells. The present vectors may be used for the production of Meltrins or any part thereof by means of genetic engineering, and used in gene therapy for Meltrins-related diseases.

[0071] The present invention therefore relates to transformants transformed by the above vectors.

[0072] The present transformants may be prepared by transforming suitable host cells by the above vectors according to known methods (e.g., Idenshi Kogaku Handbook (Handbook of gene technology), extra edition of Jikkenigaku, Yodo, 1991)). The host cells may be selected from procaryotic ones such as E.coli and Bacillus, or eucaryotic cells such as yeast, insect cells, and animal ones. The preferred transformants of the present invention are those derived from E.coli, yeast or CHO cell as a host cell to express Meltrins or the polypeptides of the present invention.

[0073] The present invention further relates to a process for producing Meltrins or the present polypeptides comprising at least any part thereof, comprising the step of culturing the above transformants.

[0074] In the present producing process, the transformants of the present invention are cultured, optionally with amplification of the gene or expression-induction, if necessary, according to known methods (e.g., Biseibutsugaku Jikkenho (Laboratory manual of microbiology), Tokyo Kagaku Dojin, 1992). The culture mixture, i.e., the cells and culture supernatant, is collected and optionally subjected to concentration, solubilization, dialysis, and various chromatography to purify Meltrins or the present polypeptides comprising any part thereof. The purification of the present polypeptides may be carried out by an optional combination of the above known methods for the purification of proteins, and an efficient purification could be performed by using an affinity column with the antibodies of the present invention.

[0075] In the present producing process, the polypeptides of the present invention may be produced by the transformants as a fused protein with other proteins such as β-galactosidase. In such case, the fused protein should be treated with chemicals such as cyanogen bromide or enzymes such as protease in a certain step in the purification process, so that the polypeptides of the present invention may be excised.

[0076] The present invention relates to medical compositions comprising a novel effective ingredient, which is Meltrins of the present invention or Meltrin-antagonist. The "Meltrin-antagonist" means a molecule which is able to inhibit fusion, adhesion or aggregation of cells through Meltrins. It includes, for example, the present antibodies recognizing Meltrins and having a neutralizing activity, the fragments of the same antibodies, the polypeptides consisting of any part of Meltrins or any combination thereof in any order, the antisense oligonucleotides for the DNAs encoding Meltrins or derivatives thereof.

[0077] The antibodies recognizing Meltrins may be prepared by the methods already mentioned in the above, and from which the antibodies which may completely or partially neutralize fusion, adhesion or aggregation of muscle cells, osteoclast or cancer cells are selected and used as the effective ingredient of the present medical composistions. The antibodies to be used as the effective ingredient include those prepared by administering any polypeptides as the antigen into any animals, as long as they may recognize human Meltrins and inhibit fusion, adhesion or aggregation of human muscle cells, osteoclast or cancer cells. They may be polyclonal or monoclonal ones, being preferably the human or humanized antibodies, considering the fact that the medical compositions will be administered to human. The human or humanized antibodies may be prepared according to the methods already described in the above.

[0078] The above fragments to be used as the effective ingredient in the present medical compositions include Fab, F(ab'), $F(ab')_2$ and Fv.

[0079] The polypeptides having any part of Meltrins or any combination thereof in any order may be used as the effective ingredient of the medical compositions, as long as they have the activity of inhibiting fusion, adhesion or aggregation of cells.

[0080] The preferable examples of the above polypeptides include those comprising a part or the whole of the disintegrin domain of Meltrins, those comprising the metalloproteinase, disintegrin and cysteine-rich regions of Meltrins, those comprising the disintegrin domain, but not comprising the transmembrane domain of Meltrins, and those comprising at least the metalloproteinase and disintegrin domains, but not comprising the transmembrane domain of Meltrins. These polypeptides may be chemically synthesized or produced by means of genetic engineering, as already mentioned in the above.

[0081] The antisense oligonucleotides or derivatives thereof to be used as the effective ingredient of the medical compositions may have any base sequences or any structure, as long as they are suitable for administration to human, and will complementarily bond to the gene for Meltrins to completely or partially inhibit their expression.

[0082] As already mentioned, Meltrins are involved in formation of osteoclast and metastasis of cancer cells. Accordingly, the medical comosition comprising the Meltrin-antagonist as the effective ingredient may be used for the purpose of inhibition of bone resorption or metastasis of cancers. The antagonist against human Meltrin α or β is more preferably used as the effective ingredient in the medical composition for inhibition of bone resorption, while the antagonist against

human Meltrin γ is more preferably used as the effective ingredient in the medical composition for inhibition of cancer metastasis.

[0083] The Meltrins or Meltrin antagonist used as the effective ingredient in the present medical composition may be formed into their salts or be modified with pharmaceutically acceptable chemical agents, as long as they will never lose their essential activities. There may be exemplilfied as the salts those with inorganic acids such as hydrochloric acid, phosphoric acid, hydrobromic acid and sulfuric acid; those with organic acids such as maleic acid, succinic acid, malic acid and tartaric acid.

[0084] The medical compositions of the present invention include those administered by any route such as oral, subcutaneous, intravenous, intramuscular, intraperitoneal, intracutaneous, and intraintestinal ones.

[0085] Any administration methods and intervals may be adopted. The present medical comopsitions may comprise depending on the administration route pharmaceutically acceptable auxiliaries such as fillers, packing agents, thickeners, binding agents, humidifying agents, disintegrating agents, surfactants, solution aids, buffers, pain-easing agents, preservatives and stabilizers. In the case of injections, for example, they may comprise stabilizers such as gelatin, human serum albumin (HSA) and polyethylene glycol; alcohols and saccharides such as D-mannitol, D-sorbitol, and glucose; and surfactants such as Polysorbate 80 (TM).

[0086] The medical compositions of the present invention may be mainly used for the prevention and treatment of osteoporosis and hypercalcemia, or the prevention of infiltration and metastasis of cancers.

[0087] The present medical compositions may be administered in an amount of about 0.1 - 100 mg/kg/day, preferably of about 1 - 50 mg/kg/day, more preferably of about 1 - 10 mg/kg/day, depending on the conditions or ages of patients, or administration routes. It may also be continuously administered by an intravenous drip, or administered by a single dose or doses at appropriate intervals per day.

[0088] The present medical compositions may be formulated according to the conventional manners. The injection, for example, may be formulated by dissolving the Meltrins or their antagonists aseptically prepared to a pharmaceutically acceptable purity into physiological saline, buffers and the like, followed by addition of gelatin or HSA, if necessary. Such injections may also be lyophilized, which will be dissolved into distilled water for the injections, physiological saline and the like when they are used.

[0089] The screening of the substances which may bind to Meltrins, inhibit the activity of Meltrins or regulate their expression may be carried out by using the Meltrins, various polypeptides, DNAs encoding them and the like.

Brief Description of Drawing

[0090]

Fig.1a - Fig.1b show the comparison between parts of mouse Meltrins α, β, γ (referred to as "Mα", "Mβ", "Mγ") and the known sequences (macrophage specific antigen (MS2), Jararhagin (JR), fertilin-α (fα).

Fig.2a - Fig.2j show the amino acid sequence of mouse Meltrin α and its corresponding DNA sequence.

Fig.3a - Fig.3j show the amino acid sequence of mouse Meltrin β and its corresponding DNA sequence, wherein "N" means unidentified base.

Fig.4a - Fig.4i show the amino acid sequence of mouse Meltrin γ and its corresponding DNA sequence. "N" means unidentified base.

Fig.5a - Fig.5j show the result of DNA sequence analysis of the DNA inserted into pBSMelα, which comprises the base sequence encoding mouse Meltrin α. "N", "M", "W" and "S" mean unidentified bases.

Fig.6a - Fig.6h show the result of DNA sequence analysis of the DNA inserted into pBSMelβ, which comprises the base sequence encoding mouse Meltrin β. "N", "M", "W" and "S" mean unidentified bases.

Fig.7a - Fig.7e show the result of DNA sequence analysis of the DNA inserted into pBSMelγ, which comprises the base sequence encoding mouse Meltrin γ. "N", "M", "W" and "S" mean unidentified bases.

Fig.8 shows schematically the structures of Meltrins α, β, γ, δMP, δPro.

Fig. 9 is a photograph of electrophoresis showing the result of Western blotting.

Fig. 10 is a photograph of electrophoresis showing the result of Northern blotting.

Fig.11a- Fig.11b show fusion-promoting activity of Meltrins for myoblast.

Fig.12a - Fig.12b show the result of base sequence analysis of the DNA inserted into pBShuMa300, which encodes human Meltrin α. "N" and"X" mean unidentified bases and unidentified amino acids, respectively.

Fig.13a - Fig.13d show the result of base sequence analysis of the DNA inserted into pBShuMγG238, which encodes human Meltrin γ.

Fig.14a shows schematically the cloning region in the cloning of human Meltrin α.

Fig.14b shows schematically the cloning region in the cloning of human Meltrin β.

Fig.15a - Fig.15f show partial amino acid sequence and its corresponding base sequence of human Meltrin α, determined based on the result of analysis of the DNA inserted into pMelα-26N, pMelα-25C.

Fig.16 shows amino acid sequence and its corresponding base sequence of human Meltrin β.
Fig.17a - Fig.17c show partial amino acid sequence and its corresponding base sequence of human Meltrin β, determined based on the result of analysis of the DNA inserted into pMelβ-24C, pMelβ-24N.
Fig.18a shows schematically the sites of the peptides administered as the antigens in mouse Meltrin α.
Fig.18b shows amino acid sequences of the peptides administered as the antigens.
Fig.19 is a photograph of electrophoresis showing the result of Western blotting with anti-mouse Meltrin α antibodies.
Fig.20 is a graph showing the inhibition of myotube formation by anti-mouse Meltrin antibodies.
Pig.21 is a graph showing the effects by anti-mouse Meltrin antibodies on the formation of pit (bone-resorption area) by mouse all bone cells.
Fig.22 is a graph showing the effects on the serum Ca values of the mouse fed with low Ca-content feed by anti-mouse Meltrin antibodies.
Fig.23a - Fig.23b show the amino acid sequence comprising the transmembrane domain of human Meltrin α and its corresponding base sequence.
Fig.24a - Fig.24e show the result of base sequence analysis of the DNA inserted into pMelβ-24C, pMelβ-24N.

Best Mode for Carrying Out the Invention

[0091] The present invention will be further illustrated by the following Examples, which should not be construed to limit the scope of the present invention.

Examples

[0092] The abbreviations used in the following description are based on the conventional ones in the art.
[0093] The processes used in the following Examples are based on Sambrook J. et al., Molecular Cloning, a Laboratory Manual 2nd ed., Cold Spring Harbor Laboratory, New York, 1989; E. Harlow, D.Lane et al., Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; and the like.

Example 1. Acquisition of the DNAs encoding mouse Meltrins by RT-PCR

(1) Preparation of RNA, cDNA.

[0094] Myogenic cell line derived from fetal fibroblast C3H10T1/2, (a clone transfected by the gene encoding "myogenin", a muscle differentiation-controlling factor and expressing the myogenin) was proliferated to the extent of 10^6 cells/ϕ 10 cm plate in DMEM supplemented with 10% fetal bovine serum (MOREGATE) and cultured at 37°C for 2 days in differentiation medium (DMEM containing 2 % horse serum from GIBCO) for differentiation and induction. Total RNA was separated according to Guanidine isothiocyanate/acid phenol method (Chomczynski P. and Sacchi N., Anal. Biochem., 162, 156-159, 1987), and poly (A) RNA was selectively separated by repeating twice oligo(dT)-cellulose column chromatography. By using the poly(A) RNA as a template and random primers (N6, Pharmacia), cDNAs were synthesized with MLV reverse transcriptase (GIBCO BRL) according to its manual for synthesis. The obtained cDNAs were then used as a template for the next PCR, and double strand DNAs were synthesized and inserted into a phage (λZapII (stratagene)) to give a cDNA library.

(2) RT-PCR

[0095] RT-PCR was carried out by using the cDNAs prepared in the above (1) as a template in the following steps:
[0096] A degenerative primer encoding the amino acid sequence EDCDCG or EECDCG was synthesized and used as a sense primer, and a degenerative primer encoding the amino acid sequence KCGKLIC was synthesized and used as an antisense primer.
[0097] The primers were mixed with the above cDNAs, Taq polymerase and the reaction agents (Boehringer Manheim), and subjected to 36 reaction cycles of 95°C for 1 min, 55°C for 2 min, and 72°C for 3 min. The amplification product of around 450 bp was then collected by 1.5% agarose gel electrophoresis.
[0098] The amplified fragments thus obtained were inserted into a SmaI site in the plasmid pBS-SKII(-) (stratagene), and subjected to DNA sequence analysis by means of a DNA sequencer (370A type, Applied Biosystems). As a result, it was found that three kinds of molecules (DNA fragments) existed (Fig.1), which were then used as a probe to screen the cDNA library so as to isolate cDNAs comprising an open reading frame with 903, 920 and 845 amino acid residues, respectively (Fig.2a - Fig.2j, Fig.3a - Fig.3j, Fig.4a - Fig.4i). The products of the respective genes were named Meltrins α, β, and γ (Fig.5a - Fig.5j, Fig.6a - Fig.6h, Fig.7a - Fig.7e). These cDNAs were inserted into pBS-SKII(-) to give the plasmids, "pBSMelα", "pBSMelβ", and "pBSMelγ", respectively.

[0099] E.coli strain JM109 was transformed according to a known method by the above plasmids "pBSMelα", "pBSMelβ", and "pBSMelγ", respectively, and the resulting transformants "JM109(pBSMelα)", "JM109(pBSMelβ)", and "JM109(pBSMelγ)" were deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on February 19, 1996 under accession numbers FERM P-15451, FERM P-15452, and FERM P-15453, respectively, and then transferred on October 8, 1996 to the deposit under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5701, FERM BP-5702, and FERM BP-5703, respectively.

(3) Analysis of the structure of Meltrins

[0100] From the structure analysis of Meltrins on the basis of the DNA sequences determined in the above (2), it was supposed that Meltrins α, β, and γ were a transmembrane-type protein consisted of an extracellular domain, transmembrane (TM) domain, and intracellular domain, and that the extracellular domain consists of a precursor domain (pro region) comprising a signal peptide-like sequence, metalloproteinase domain, disintegrin domain, and the following cysteine-rich region. A fusion peptide-like sequence was contained in the cysteine-rich domain of Meltrin α (Fig.8).

[0101] Based on their homology to the snake venom, Jararhagin, it has been considered that in Meltrin α, the precursor domain corresponded to the sequence from N-terminal to Arg (No.205) and to the bases No.221-835, the metalloproteinase domain to the sequence from Glu (No.206) to Pro (No.414) and to the bases No.836-1462, the disintegrin domain to the sequence from Phe (No.420) to Gly (No.509) and to the bases No.1478-1747, the cysteine-rich region to the sequence from His (No.510) to Gly (No.706) and to the bases No.1748-2338, the fusion peptide-like sequence to the sequence from Gly (No.585) to Glu (No.607) and to the bases No.1973-2041, the transmembrane domain to the sequence from Leu (No.707) to Leu (No.727) and to the bases No.2339-2401.

[0102] Similarly, it was considered that in Meltrin β, the precursor domain corresponded to the sequence from N-terminal to Arg (No.204) and to the bases No.63-674, the metalloproteinase domain to the sequence from Glu (No.205) to Pro (No.409) and to the bases No.675-1289, the disintegrin domain to the sequence from Tyr (No.415) to Gly (No. 504) and to the bases No.1305-1574, the cysteine-rich region to the sequence from Thr (No.505) to Pro (No.706) and to the bases No.1575-2180, the transmembrane domain to the sequence from Val (No.707) to Arg (No.729) or to Leu (No.724) and to the bases No.2181-2249 or 2181-2234.

[0103] Similarly, it was considered that in Meltrin γ, the precursor domain corresponded to the sequence from N-terminal to Arg (No.205) and to the bases No.69-683, the metalloproteinase domain to the sequence from Ala (No.206) to Pro (No.406) and to the bases No.684-1292, the disintegrin domain to the sequence from Tyr (No.412) to Gly (No. 502) and to the bases No.1302-1574, the cysteine-rich region to the sequence from Tyr (No.503) to Ala (No.694) and to the bases No.1575-2150, the transmembrane domain to the sequence from Leu (No.695) to Ile (No.714) and to the bases No.2151-2210.

Example 2: Establishment of anti-Meltrin α antibodies

(1) Preparation of immunogen

[0104] A chimera polypeptide was prepared as follows, which consisted of glutathione-S-transferase (GST) (Smith, D.B. & Johnson, K.S., Gene, Vol.67, 31-40, 1988) and the polypeptide having the amino acid sequence from Ser (No. 483) to Lys (No.635) of Meltrin α in Fig.2a - Fig.2j, said polypeptide being attached to the C-terminal of GST. First, the plasmid, pGEX2T (Pharmacia) comprising the cDNA encoding GST was digested at a BamHI site and used as a vector. On the other hand, the cDNA corresponding to the amino acid sequence from Ser (No.483) to Lys (No.635) of Meltrin α in Fig.2a - Fig.2j was amplified from pBSMelα by PCR, and ligated with a BamHI linker by a DNA ligase. The resulting cDNA was then ligated with the above vector by a DNA ligase to give a plasmid, which was then tranformed into E.coli strain NM522.

[0105] The transformed E.coli was cultured in L-broth with 1mM IPTG to produce a large amount of the chimera polypeptide in the inclusion bodies upon expression-induction. The strain was suspended into MTPBS (150mM NaCl, 16mM Na_2HPO_4, 4mM NaH_2PO_4, 0.1mM PMSF), subjected to ultrasonication, and solubilized with 1% Triton. The supernatant of the thus treated mixture was collected. Glutathione agarose (Sigma) was mixed with the supernatant to adsorb the chimera polypeptide which was then eluted with an elution buffer (50mM Tris-HCl, pH 8.0, 0.5mM glutathione) and used as an immunogen.

(2) Preparation of antiserum

[0106] The antigen (1mg) prepared in the above (1) in 0.5ml PBS and RIBI in PBS 0.5ml (MPL+TDM+CWS Emulsion,

Funakoshi) was mixed with each other, and subcutaneously or intracutaneously administered into a rabbit (12 weeks old, female). After boosting three times with 500μg dose at 4 week intervals, the blood was collected and serum was separated to give antiserum.

(3) Affinity purification of antiserum

[0107] The chimera polypeptide expressed in E.coli and solubilized in the above (1), or GST having no fused polypeptide was bound to the glutathione agarose beads. The resulting beads were washed with 0.2M sodium borate (pH 9.0), and mixed with dimethyl pimelidiate (a final concentration of 20mM) so that the antigen was irreversibly bound to the beads, so as to give chimera polypeptide-affinity beads and GST-affinity beads, respectively.

[0108] The antiserum diluted ten times with 10mM Tris-HCl (pH 7.5) was first mixed with the GST-affinity beads for anti-GST antibodies to be absorbed and removed, and then mixed with chimera polypeptide-affinity beads for anti-Meltrin α antibodies to be adsorbed thereon. The resulting chimera polypeptide-affinity beads were washed with 10mM Tris (pH 7.5) and 500mM NaCl, and the anti-Meltrin α antibodies were eluted with 100mM glycine and collected as purified anti-Meltrin α antibodies.

(4) Western blotting

[0109] C2 cell was proliferated to the extent of 10^6 cells/ϕ 10cm plate in DMEM supplemented with 15% fetal bovine serum, then cultured at 37°C in differentiation medium (DMEM supplemented with 2% horse serum) and collected on the second day (C2DM d2) and on the 4th day (C2DM d4).

[0110] Further, C2 cell transformed by pBOSMelα (+) prepared in the following Example 5 (3) was cultured in DMEM supplemented with 15% fetal bovine serum at 31°C for three days, inoculated into a plastic dish (ϕ 6cm) at a density of 2×10^5/dish, further cultured for one day and transferred into the above differentiation medium for differentiation induction. After two day-culture in the differentiation medium, the cells were collected.

[0111] The collected C2DM d2, C2DM d4 or transformants by pBOSMelα (+) was mixed with SDS solubilizing buffer (100mM Tris-HCl (pH 6.8), 4% SDS, 20% Glycerol), subjected to ultrasonication and centrifuged to give their supernatant as a sample.

[0112] A membrane was wahsed twice with a washing solution. The antiserum prepared in the above (3) was diluted 20 times with 5% skim milk solution in TBS-T, into which the membrane was soaked and incubated at 37°C for one hour. After the incubation, the membrane was washed twice with the washing solution. The membrane was then soaked into a biotin-labelled anti-rabbit immunoglobulin antibody (Daco) diluted 4,000 times with the above skim milk solution and incubated at 37°C for one hour. After the incubation, the membrane was washed twice with the washing solution. The membrane was reacted with a peroxidase-labelled streptoavidin for one hour, washed twice, stained with MB reagent (Cat.TM912, Shic) and detected by ECL system (Amersham).

[0113] The results are shown in Fig.9.

[0114] The Western blotting revealed the bands at about 115KD, 86KD, 67KD, and 58KD, indicating that Meltrin α was expressed as a glycoprotein. It was also considered that the precursor domain was deleted in the molecule of 86KD, and both the precursor and metalloproteinase domains were deleted in the molecule of 67KD or 56KD.

Example 3: Northern blotting

[0115] Poly $(A)^+$ RNAs were prepared from vaious tissues of mouse (bone, brain, liver, heart and skeletal muscle of adult mouse; bone and skeletal muscle of newborn mouse; and bone and skeletal muscle of fetal mouse) by using a mRNA purification kit of Pharmacia according to the method described in Example 1. RNAs were denatured by heating at 65°C for 5 min in 50% formamide, subjected to elecrtophoresis on 1.5% agarose gel comprising 6.6% formalin, and transferred onto a nylon membrane (Highbond-N, Amersham).

[0116] On the other hand, cDNAs encoding a part of the disintegrin and cysteine-rich regions (Glu(No.434) - Cys(No. 583) in Fig.2a - Fig.2j, Glu(No.429) - Cys(No.578) in Fig.3a - Fig.3j, Glu(No.426) - Cys(No.575) in Fig.4a - Fig.4i) were prepared by PCR, and labelled with ^{32}P using a random primer labelling kit (Megaprime, Amersham). As a control probe, cDNA encoding G3PDH (glyceraldehyde 3-phosphate dehydrogenase) was also llabelled with ^{32}P in the same way. The above mRNAs were hybridized with the radiolabelled cDNAs under high stringency conditions according to the method of Sambrook J.et al. (Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Habor Laboratory, New York, 1989).

[0117] Their results are shown in Fig. 10.

[0118] Fig.10 has revealed that Meltrin α and β were expressed only in bones of adult and newborn mouses, and skeletal muscles of newborn and fetal mouses (the results from the fetal mouse are not shown in Fgi.10). There was no tissue-specificity in the expression of Meltrin γ, since it was universally expressed in all the tissues.

Example 4: Confirmation of adhering activity of Meltrin α

(1) Construction of plasmids pBOSMelαδMP(+) and pBOSMelαδMP(-)

[0119] A deletion type Meltrin δMP wherein the precursor and metalloproteinase domains in the extracellualr domain of Meltrin α had been deleted was prepared in the followig method.

[0120] The plasmid, pBSMelα was partially digested at MscI and subjected to electrophresis on 1% agarose gel to give a linear plasmid DNA. The resulting DNA was partially digested at NheI, treated with a Klenow fragment to generate blunt ends, and subjected to intramolecular ligation. Vectors having the right deletion were selected and their DNA sequences were confirmed. After digestion at multicloning sites of EcoRV and NotI in the vectors, a deletion type δMP fragment of about 5.8kb was obtained.

[0121] On the other hand, the plasmid, pEFBOS (Mizushima S. & Nagata S, Nucleic Acid Res. Vol.18, p.5322, 1990) was digested by a restriction enzyme XbaI, dephosphorylated, treated with a Klenow fragment to generate blunt ends and subjected to electrophresis on 1% agarose gel to give a linear plasmid DNA. The resulting linear DNA was then ligated with the above fragment of about 5.8kb by a DNA ligase to give the plasmids pBOSMelαδMP(+) and pBOSMelαδMP(-). They were the constructs comprising the inserted DNA encoding the δMP fragment wherein the amino acid sequence of from Ile(55) to Glu(399) of Meltrin α was deleted, in sense direction and antisense direction, respectively.

(2) Construction of plasmid pBOSMelα(+)

[0122] The plasmid, pBSMelα, was partially digested by EcoRV and NotI to give a fragment of about 7kb. The above pEFBOS plasmid was digested by a restriction enzyme XbaI, dephosphorylated, treated with a Klenow fragment to generate blunt ends, and subjected to electrophresis on 1% agarose gel to give a linear plasmid DNA. The resulting linear DNA was then ligated with the above fragment of about 7kb by a DNA ligase to give the plasmids pBOSMelα(+).

(3) Preparation of plasmid pBOSMelαδPro(+)

[0123] There was a AflII site in the boundary region between the precursor and metalloproteinase domains of Meltrin α, and there was a NheI site in the boundary region between metalloproteinase and disintegrin domains of Meltrin α. On the other hand, there remined the NheI site in the boundary region between the signal peptide-like sequence and disintegrin domain in pBOSMelαδMP(+) prepared in the above (1). Accordingly, pBOSMelα was digested at AflII, ligated with a NheI linker immediately before its metalloproteinase domain and digested at NheI, so that the metalloproteinase would be excised. The excised domain was inserted into the NheI site between the signal peptide-like sequence and the disintegrin domain of pBOSMelαδMP(+) to give the expression plasmid, pBOSMelαδPro(+) encoding δPro wherein there a deletion was found around the precursor domain (the amino acid sequence of from Ile(No.55) to Glu(No.206) of Meltrin α).

(4) Confirmation of myoblast fusion-promoting activity

[0124] Myoblast cell line C2 was transfected by the mixture comprising the plasmid pBOSMelα(+) or pBOSMelαδMP (+), and the plasmid pSV2NEO in a molar ratio of 20:1 by using LIPOFECTAMINE (Gibco BRL) according to its protocol. The transfected cells were diluted and inoculated on a plate (ϕ 10cm) coated with collagen (IWAKI) so that the transformants would be obtained at a density of 10 - 20 clones per plate. The inoculated cells were cultured for 12 days in DMEM containing 20 % fetal bovine serum and 5 ng/ml of bFGF (Gibco BRL) followed by isolation thereof.

[0125] For the purpose of the examination of myoblast fusion-promoting activity, the resulting transfomants and the parent strain C2 were cultured for 3-4 days in the absence of bFGF, inoculated onto a plastic dish (ϕ 6cm) at a density of 2 x 10^5/dish, and further cultured for one day, followed by the 4 day culture in the above differentiation medium for differentiation induction. Upon differentiation induction, C2 began to form myotube. After the 4 day culture followed by fixation with methnol and staining with Giemsa and Wright's reagents (Merck), the number of nuclei were determined at any four independent fields of 1 mm^2 on the dish and fusion index was calculated as follows:

Fusion Index = 100 * (The number of nuclei in multicleate syncytium having three or more nuclei) / (The number of the total nuclei)

[0126] Further, the time course of the fusion index was observed after differentiation induction every one day for five days.

[0127] The results are shown in Fig.11a - Fig.11b. As seen from these figures, the fusion activity of the transfomant expressing the full length of Meltrin α (pBOSMelα(+) which was referred to as "full length" in Fig.11a) become lower than that of the parent cell, and it was therefore considered that the full length of Meltrin α would suppress the cell fusion in some way. On the other hand, the transfomant harboring pBOSMelαδMP(+), which was referred to as "ΔMP" in the figures, significantly promoted the cell fusion activity. It was also observed that the transformant harboring pBOSMelαδPro (+) promoted the cell fusion activity.

[0128] On the other hand, the C2 cell transformed by the plasmid pBOSMelβ(+) prepared by the insertion of the DNA encoding the full length of Meltrin β in the same way as in the above (2) could not cause any significant change in the fusion activity for muscle cells. However, The C2 transformant cotransfected by pBOSMelα(+) and pBOSMelβ(+) promoted the cell fusion activity compared with that of parent cell.

[0129] On the other hand, neither the C2 cell transformed by the plasmid pBOSMelγ(+) prepared by the insertion of the DNA encoding the full length of Meltrin γ in the same way as in the above (2), nor the C2 transformant cotransfected by pBOSMelα(+) and pBOSMelγ(+) could cause any significant change in the fusion activity for muscle cells.

[0130] These results demonstrate that Meltrin α is involved in the fusion of muscle cells, and will show its activity to promote the cell fusion upon its processing. It is estimated that Meltrin α or Meltrin β does not act alone, but act in the form of a heteromer between them, since the transfomant expressing both Meltrin α and Meltrin β promoted the fusion of muscle cells.

(5) Examination of the function of Meltrins in non-muscle cells

[0131] The mouse fibroblast L929 was transformed by pBOSMelα(+) or pBOSMelβ(+) and the transformants expressing Meltrin α or Meltrin β were isolated. These transfomants did not aggregate, nor fuse with each other. This was also true for the case of the transformant expressing both Meltrin α and Meltrin β.

[0132] On the othe hand, the L929 cells transformed by pBOSMelγ(+) could showed a significant aggregation activity upon the addition of calcium ion, after the cells had been torn from a plate in a medium comprising no calcium ion.

[0133] These results demonstrate that Meltrin γ has a cell aggregation activity, and by considering the similarity of these molucules it is suggested that myoblast fusion-promoting activity of Meltrin α and Meltrin β may be attributed to their myoblast aggregation-promoting activity.

Example 5: Inhibition of adhering activity by antisense

[0134] The plasmid BOSMelαδMP(-) prepared in Example 4 (1) was mixed with the plasmid PSV2NEO at a molar ratio of 20:1, by which C2 cells were tranformed according to the method of Example 4 (4) followed by isolation of the transfomants expressing antisense RNA. The adhering activity of the thus isolated transfomants was determined by the method of Example 4. The results are shown in Fig.11a - Fig.11b, which demonstrated that the fusion of C2 cells was inhibited by the expression of antisense RNA for δMP (referred to as "AS" in the figures).

[0135] The above results have revealed that Meltrin α plays an essential role in the cell fusion of muscle cells.

Example 6: Preparation of cDNA fragments encoding human Meltrins α and γ

[0136] By using mRNA purified from human myelocytes (Clonetech Co.) as a template, cDNAs were prepared according to the method of Example 1 (1), and 36 cycles of PCR was then carried out by using the degenerative primer obtained in Example 1 (2) and said cDNAs as a template. The amplified product was inserted into a EcoRV site of pBS-SKII(-), and named "pBShuMα300." The results of DNA sequencing are shown in Fig.12a and Fig.12b.

[0137] It was found that the DNA sequence comprised the base sequence encoding the part from an intermediate position of the disintegrin domain to an intermediate position of the cysteine-rich region of human Meltrin α (the disintegrin domain is located to Gly (No.36), followed by the cysteine-rich region in Fig.12a and Fig.12b).

[0138] On the other hand, by using a part of a human sequence (D-14665) registered with a data base, whose function had not yet identified, a senseprimer (5'-CACGATGATGGGAGAGATTG-3') and antisense primer (3'-CACTCTGATTTCCTATGCCTC-5') were synthesized. PCR was carried out according to the above method to give the amplified product, which was then inserted into the EcoRV site of pBS-SKII(-), and named "pBShuMyG238." The results of DNA sequencing are shown in Fig.13a and Fig.13b.

[0139] It was found that the DNA sequence comprised the base sequence encoding the part from an intermediate position of the metalloproteinase domain to an intermediate position of the cysteine-rich region of human Meltrin γ (the metalloproteinase domain is located from N-termial to Pro (No.40), the disintegrin domain from Lys (No.41) to Gly (No. 136) or from Tyr (No.46) to Gly (No.136), followed by the cysteine-rich region from Tyr (No.137)). The E. coli strain JM109 was transfomed by those plasmids to give JM109(pBShuMα300) and JM109(pBShuMγG238), which were deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology

(1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on February 19, 1996 under accession numbers FERM P-15454 and 15455, respectively, and then transferred on October 8, 1996 to the deposit under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5704 and 5705, respectively.

Example7: Preparation of cDNA fragment encoding human Meltrin α by usig cDNA library derived from human placenta -1

(1) First screening

[0140] Based on the cDNA sequence of Meltrin α obtained in Example 6, sense primer MA-1 and antisense primer MA-2 were synthersized (see Table 1). The human placenta λgt11 cDNA library (Clonetech Co., code No. CLHL1008b) was inoculated onto LB plate (ϕ 10cm) at such a density that 10,000 plaques per plate may be obtained. After the formation of plaques, SM buffer 5ml was added to each plate, the plates were put by incubation at a room temperature for 4 hours, and phages were collected from each plate (plate lysate method). PCR was carried out by using the collected phage solution as a template. Thus, mA-1 and MA-2 primers, Ex Taq polymerase (TaKaRa Co.,), and its reagents (TaKaRa Co.,) were mixed, followed by 35 cycles of the reactions at 94°C for 30sec, 55°C for 30sec, and 72°C for one min. A part of the amplified products was subjected to an agarose gel electrophoresis, and a phage solution of the clone comprising Meltrin α cDNA was selected.

(2) Second screening

[0141] The phage solution of the desired clone obtained in the first screening was inoculated at such a density that 400 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(3) Third screening

[0142] The phage solution of the desired clone obtained in the second screening was inoculated at such a density that 40 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(4) Forth screening

[0143] The phage solution of the desired clone obtained in the third screening was inoculated at such a density that 10 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(5) Final screening

[0144] The phage solution of the desired clone obtained in the forth screening was inoculated at such a density that 20 plaques per plate may be obtained. After the formation of plaques, each plaque was stuck with a toothpick, and the sticking material was suspended as a template into PCR solution. The above 35 cycles of the PCR with MA-1 and MA-2 primers finally gave two psitive clones. A single positive plaque comprising the desired clone was collected in SM buffer, and the phage was lysed thereinto.

[0145] PCR was carried out by using λgt11 Forward primer and λgt11 Reverse primer (Table 1) to give a fragment of human Meltrin α cDNA in the phage vector.

[0146] From a partial DNA sequencing of the terminal bases of the resulting fragments it was estimated that those cDNAs comprised the base sequences encoding human Meltrin α obtained in Example 6, and corresponded to about 650 amino acids (Clone 23) or about 500 amino acids (Clone 25) of mouse Meltrin (Fig. 14).

Example 8: Preparation of cDNA fragment encoding human Meltrin α by usig cDNA library derived from human placenta -2

[0147] A sense primer Mel α-5'S was designed based on the sequence encoding the N-terminal of the cDNA sequence of the clone 23 revealed in Example 7. The human placenta λgt11 cDNA library (Clonetech Co.) was screened by the sense primer Mel α-5'S and antisense primer MA-2 to give cDNA encoding about 700 amino acids (Clone 26) (Fig.14a). For the purpose of the analysis of the base sequence of Meltrin gene, the four primers, λgt11 Forward-Eco, λgt11

Reverse-Eco, MA-1-Eco, and MA-2-Eco were synthesized (Table 1).

[TABLE 1] The base sequences of the primers for PCR

MA-1	: 5' ACG ATG GGC ACT CAT GTC AG 3'
MA-2	: 5' CAT CTC GCA TTT GGC AAA GG 3'
λ gt11 Forward	: 5' GGT GGC GAC GAC TCC TGG AGC CCG 3'
λ gt11 Reverse	: 5' TTG ACA CCA GAC CAA CTG GTA ATG 3'
Mel α-5'*S*	: 5' CAC TGA ACA TTC GGA TCG TG 3'
λ gt11 Forward-Eco	: 5' CCG GAA TTC GGT GGC GAC GAC TCC TGG AGC CCG 3'
λ gt11 Reverse-Eco	: 5' CCG GAA TTC TTG ACA CCA GAC CAA CTG GTA ATG 3'
MA-1-Eco	: 5' CCG GAA TTC ACG ATG GGC ACT CAT GTC AG 3'
MA-2-Eco	: 5' CCG GAA TTC CAT CTC GCA TTT GGC AAA GG 3'
S-hMel α-TM5'	: 5' GCA CAA AGT GTG CAG ATG GA
A-mMel α-3'	: 5' CAG AGG CTT CTG AGG AGG N

[0148] The second half of the Meltrin gene was amplified by PCR using Clone 25 as a template, and MA-1-Eco and λgt11 Reverse-Eco primers. The first half of the Meltrin gene was amplified by PCR using Clone 26 as a template, and MA-2-Eco and λgt11 Forward-Eco primers. These cDNA fragments were digested at EcoRI and cloned into the EcoRI site of pUC 118 to give the plasmid vectors "pMelα-26N" and "pMelα-25C", respectively. The sequences of Meltrin α cDNA comprised in these plasmids were determined by a conventional method.

[0149] The E.coli strain JM109 was transfomed by those plasmids according to the known method of Hanahan et al. to give JM109(pMelα-26N) and JM109 (pMelα-25C), and were deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on October 3, 1996 under the terms of the Budapest Treaty on the International Recognition of the Deposit of microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5689 and 5688, respectively.

[0150] The base sequence and its corresponding amino acid sequence of human Meltrin α which had been revealed by the base sequencing of pMelα-26N and pMelα-25C are shown in Fig.15a - Fig.15f.

[0151] Comparison of the DNA sequence thus obtained with that obtained in Example 6 indicated four discrepancies in base pairs, the three of which being silent mutation, and the other dicrepancy causing substitution of Asp (No.505) in the above figures for Glu in the sequence of Example 6.

[0152] The analysis of the structure of the base sequence showed that the DNA encoded the sequence from an intermediate part of the precursor domain to the C-termial of Meltrin α. Thus, it has been considered that in the amino acid sequence shown in Fig.15a - Fig.15f, the partial sequence (C-terminal) of the precursor domain corresponds to the the sequence from Gly N-terminal to Arg (No.155) and to the bases No.1-465, the metalloproteinase domain to the sequence from Glu (No.156) to Pro (No.364) and to the bases No.466-1092, the disintegrin domain to the sequence from Glu (No.365) or Phe (No.370) to Gly (No.459) and to the bases No.1093 or 1108-1377, the cysteine-rich region to the sequence from His (No.460) to Gln (No.656) or Ala (No.652) and to the bases No.1378-1968 or 1956, the fusion peptide-like sequence to the sequence from Gly (No.535) to Gln (No.557) and to the bases No.1603-1671. There was no transmembrane domain in this sequence, suggesting that human Meltrin α existed as a soluble protein without a transmembrane domain in a body. In other words, it is considered that Meltrin α having the amino acid sequence of Fig. 15a - Fig.15f is extracellularly secreted and present in blood or body fluid. It is considered that such soluble Meltrin α takes a part in regulating adhesion, fusion and aggregation of cells in the body.

[0153] It is considered that Meltrin α having the amino acid sequence of Fig.15a - Fig.15f has generated as a result of an alternative splicing of the gene. It is also considered that the DNA encoding the region downstream of the cysteine-rich region, and the DNA encoding transmembrane doamin and intracellular domain are located on different exons, and that the splicing out of either DNA would yield a soluble type Meltrin, or a membrane-binding type Meltrin.

Example 9: preparation of cDNA fragments encoding human Meltrins β

(1) Preparation of cDNA fragment encoding a part of the disintegrin domain of human Meltrin β

[0154] By using mRNA purified from human myelocytes (Clonetech Co.) as a template, cDNAs were prepared according to the method of Example 1 (1), and 36 cycles of PCR were then carried out by using the degenerative primers obtained in Example 1 (2) and said cDNAs as a template. The amplified product was inserted into pBS-SKII(-). The analysis of the resulting DNA sequence revealed that it was a partial sequence of Meltrin β. The determined DNA

sequence is shown in Fig.16.

(2) First screening by using cDNA library originated in human fetal lung

[0155] Based on the partial cDNA sequence of Meltrin β obtained in the above (1), sense primer MA-3 and antisense primer MA-4 were synthersized (see Table 2). The human fetal lung λgt11 cDNA library (Clonetech Co., code No. CLHL1072) was inoculated onto LB plate (φ 10cm) at such a density that 10,000 plaques per plate may be obtained. After the formation of plaques, SM buffer 5ml was added to each plate. And the plates were put at a room temperature for 4 hours, and phages were collected from each plate (plate lysate method). PCR was carried out by using the collected phage solution as a template. Thus, MA-3 and MA-4 primers, Ex Taq polymerase (TaKaRa Co.,), and its reagents (TaKaRa Co.,) were mixed, followed by 35 cycles of the reactions at 94°C for 30sec, 55°C for 30sec, and 72°C for one min by means of DNA thermal cycler (Perkin Elmer Co.,). A part of the amplified products was subjected to an agarose gel electrophoresis, and a phage solution of the clone comprising Meltrin β cDNA was selected.

(3) Second screening

[0156] The phage solution of the desired clone obtained in the first screening was inoculated at such a density that 1000 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(4) Third screening

[0157] The phage solution of the desired clone obtained in the second screening was inoculated at such a density that 100 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(5) Forth screening

[0158] The phage solution of the desired clone obtained in the third screening was inoculated at such a density that 10 plaques per plate may be obtained. After the formation of plaques, phages were collected in the same manner as above and a phage solution comprising the desired clone was selected.

(6) Collection and confirmation of DNA fragment comprising partial cDNA sequence

[0159] The PCR was carried out using the phage solution of the desired clone obtained in the forth screening (#24) as a template, and a combination of λgt11 Forward primer (Table 1) and MA-4 primer or a combination of λgt11 Reverse primer (Table 1) and MA-3 primer to give amplified products with about 500bp (24-F/4) and about 5kbp (24-R/3), respectively. From a partial DNA sequencing of the terminal bases of the resulting two DNA fragments, it was estimated that those cDNA comprised the base sequences determined in the above (1).

(7) Analysis of base sequences

[0160] For the purpose of subcloning of the cDNA fragments comprising the cDNA partial sequence of human Meltrin β, two primers MA-3-Eco and MA-4-Eco were newly synthersized (see Table 2).

[0161] The PCR was carried out using the phage solution (#24) as a template, and a combination of λgt11 Forward-Eco primer (Table 1) and MA-4-Eco primer or a combination of λgt11 Reverse-Eco primer (Table 1) and MA-3-Eco primer. The resulting amplified products were digested with EcoRI and inserted into the EcoRI site of pUC118 to give the plasmids, "pMelβ-24C" and "pMelβ-24N", respectively. The sequence of Meltrin β cDNA comprised in these plasmids was determined by a conventional method.

[0162] The E. coli strain JM109 was transfomed by those plasmids according to the known method of Hanahan et al. to give JM109(pMelβ-24C) and JM109 (pMelβ-24N), and were deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on October 3, 1996 under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5690 and 5691, respectively.

[0163] The base sequence and its corresponding amino acid sequence which had been revealed by the base sequencing of pMelβ-24C and pMelβ-24N are shown in Fig.24a - Fig.24e.

[0164] Comparison of the DNA sequence thus obtained with that obtained in the above (1) showed one discrepancy

in base pairs, which was a silent mutation, causing no change of amino acid.

[0165] The analysis of the structure of the base sequence showed that the DNA encoded the sequence from an intermediate part of the metalloproteinase domain to the C-termial of human Meltrin β. Thus, it has been considered that in the sequence shown in Fig.24a - Fig.24e, the partial sequence at C-terminal of the metalloproteinase domain corresponds to the the sequence from Gly (N-terminal) to Pro (No.36) and to the bases No.2-109, the disintegrin domain to the sequence from Asp (No.37) or Tyr (No.42) to Gly (No.131) and to the bases No.110 or 125-394, the cysteine-rich region to the sequence from Thr (No.132) to Pro (No.330) and to the bases No.395-991, the transmembrane domain to the sequence from Val (No.331) to Met (No.348) or Arg (No.353) and to the bases No.992-1045 or 1060. It is considered that the sequence from Tyr (No.349) or Gln (No.354) corresponds to the intracellular domain. However, as homology analysis to mouse Meltrin β shows a very low homology in the sequence from Pro (No.395), it is estimated that the sequence up to His (No.394) is involved in the function of extracellular domain of human Meltrin β. The sequence up to Pro (No.395) in Fig. 24a - Fig.24e is shown in Fig.17a - Fig.17c.

[TABLE 2] The base sequences of the primers for PCR

MA-3	: 5' TGC TGC CAC CAG TGT AAG 3'
MA-4	: 5' TCC TGG TAG GTG AGG CAC ATG 3'
MA-3-Eco	: 5' CCG GAA TTC TGC TGC CAC CAG TGT AAG 3'
MA-4-Eco	: 5' CCG GAA TTC TCC TGG TAG GTG AGG CAC ATG 3'

Example 10: Preparation of anti-Meltrin α monoclonal antibodies

(1) Selection of peptides

[0166] Based on the amino acid sequence of mouse Meltrin α determined in Exmple 1, their epitopes were analysed.

[0167] Eight kinds of peptide sequences were selected as a potential epitope, based on the secondary structure estimated from the regions wherein discrepancy in amino acids is seen between Meltrins α and β, the estimated non-RGD region, and the region wherein metalloproteinase had been cleaved (Fig.18a and b). These eight kinds of peptides were synthesized by Peptide Synthesizer (ABI 432A) so that they would have Cys at their C-terminal, cleaved, and purified by HPLC of a reverse phase column (YMC-ODS).

(2) Preparation of antiserum

[0168] After lyophilization of the peptides obtained in the above (1), each peptide 0.55mg was dissolved in 0.1 M phosphate buffer (pH 7.0) 55μl. Maleimidated KLH (Boehringer Manheim) 0.77mg was dissolved in distilled water 77μl. The two resulting solutions were combined, and reacted at a room temperature for two hours, followed by the purification by Nick column (Pharmacia) equilibrated with physiological saline to give antigens to be used in the following experiments.

[0169] Each antigen 50μg was diluted with physiological saline to 0.1 ml, mixed with the same amount of Freund's complete adjuvant (DIFCO) and administered intraperitoneally into Wistar rat (5 weeks old, female). The antigen was mixed with the same amount of Freund's incomplete adjuvant (DIFCO) and administered two weeks later in the same way as above.

(3) Evaluation of antiserum (plate assay)

[0170] After one week from the administration, the blood was drawn from the eyeground of the rat, and an increase of the antibody titer for the administered peptides was confirmed by the reaction between immobilized peptides and the antiserum according to a plate assay as follows.

[0171] First, 50mM phosphate buffered saline (0.9% NaCl, pH 7.2) comprising 0.5mg/ml of Sulfo-SMCC (Pierce) was poured into each well of an amino plate (Sumitomo Bakelite). After incubation at 37°C for 2 hours, the wells were washed five times with ion-exchanged water, and the above buffer comprising 0.5μg/ml of each peptide was added. After incubation at 37°C for one hour, the well were blocked by 0.076M phosphate buffered saline (0.45% NaCl, pH 6.4), which will be referred to hereinafter as "PBS", comprising 0.1% of BSA and 4mg/ml of cysteamine. The blocking agent was removed, each antiserum diluted 1,000 to 100,000 times with PBS was added followed by incubation at 37°C for one hour. After two repeats of washing of the wells with 0.9% NaCl comprising 0.005% Tween20, an anti-rat immunoglobulin abtibody labelled with peroxidase (Dako) and diluted with PBS comprising 10% rabbit serum was added to each well followed by incubation at 37°C for one hour. Upon the completion of the reaction, the wells were washed five times with

a washing liquid and two times with ion-exchanged water. And 0.1M McIlvaine buffer (pH 5.0) comprising 3mg/ml of o-phenylene diamine and 0.027% hydro peroxide was added and reacted for 5min. The reaction was terminated by the addition of 1N HCl, and absorbance at 490nm was measured. The results are shown in Table 3, in which (++) means a strong reactivity, and (+) means a week reactivity.

TABLE 3 Reaction of antiserum with the peptide antigens

peptide antigens	Reaction of Antiserum
1 ProA	++
2 MP-A	++
3 MP-B	++
4 DC-A	+
5 DC-B	+
6 DC-C	++
7 DC-D	N.D.
8 DEA	++

N.D. (not determined)

(4) Evaluation of antiserum (Western blotting)

[0172] For the confirmation of the binding of the antiserum prepared in the above (2) to Meltrins, Western blotting was carried out.

[0173] Mouse myoblast C2 was transformed by pBOSMelαδPro(+) and pBOSMelβ(+), which will be referred to hereinafter as "#9-3", and mouse myoblast C2 was transformed by pBOSMelαδMP(+), which will be referred to hereinafter as "#3-5."

[0174] The transformed C2 cells of 1 x 10^7 cells were washed with PBS-(GIBCO BRL) and collected by centrifugation. The density of the collected cells was adjusted to 5 x 10^6 cells/ml, mixed with a proteolysis inhibitor, Cϕmplete (Boehringer Manheim) in amount of one 25th of the volume of the cell-mixture, and mixed with SDS to a final concentation of 0.2%. After incubation at a room temperature for 30min, the cells were subjected to sonication at 4°C for 10sec (Isec x 10), and centrifuged. The resulting supernatant was collected and used as a cell lysate. Another cell lysate was prepared from fibroblast L929 (ATCC No.CCL-1) in the same way, and used as a negative control.

[0175] The resulting cell lysate (10μl) was mixed with an equiamount of a gel loading buffer (0.25M Tris-HCl, 2% SDS, 30% Glycerol, 0.01% BPB(pH 6.8)), the resulting solution (6μl) was applied to SDS-PAGE of 4-20T % (Tefco), and electrophoresed under 25mA at a room temperature for about one hour. After the completion of the electrophoresis, the contents were transferred to PVDF membrane (Millipore) under the conditions of 150mA, 4°C and 45min. The membrane was blocked by shaking in 4% skim milk (Meiji Milk Co.) at a room temperature for one hour, and each lane was cut. Each excised lane was soaked and shaked in antiserum (1ml) diluted 500 times with 50mM Tris-HCl (pH 7.2) comprising 0.05% Tween20 (referred to hereinafter as "T-TBS") and 4% skim milk at a room temperature for one hour. After the completion of the reaction, each lane was washed two times with T-PBS, soaked in 1ml of an anti-rat immunoglobulins antibody labelled with HRPO (Dako) diluted 500 times with T-PBS comprising 4% skim milk, and reacted at a room temperature for one hour. After washing five times with T-PBS, it was detected by ECL system (Amersham). The results are shown in Table 4. Bands were detected in the three kinds of the antiserums by the Western blotting.

TABLE 4 Reaction of antiserum with the cell lysate in Western blotting

Peptide antigens	Western blottting
1 ProA	+
2 MP-A	-
3 MP-B	-
4 DC-A	N.D.
5 DC-B	N.D.
6 DC-C	+
7 DC-D	N.D.

(continued)

Peptide antigens	Western blottting
8 DEA	+
N.D. (not determined)	

(5) Preparation of monoclonal antibody

[0176] The antigens (ProA, MP-B, DC-C, DEA) (50μg each) were diluted with 400μl of physiological saline, and injected into the tail vein of the rats whose antibody titer had increased. Three days later, cell fusion was carried out by using myeloma P3X63Ag8U.1 according to the known method (Monoclonal antibody Jikken Sosa Nyumon (Guide of monoclonal antibody preparation), Tamie Ando and Jo Chiba, Koudan-sha Scientific). Six days later, the culture supernatant was collected and subjected to the plate assay according to the method of the above (3). The wells that showed reactivity with the peptide antigens were subjected to cloning by limiting dilution(Monoclonal antibody Jikken Sosa Nyumon (Guide of monoclonal antibody preparation), Tamie Ando and Jo Chiba, Koudan-sha Scientific). After cloning, the screening by the plate assay was performed again to give 27 clones of the hybridomas producing an anti-mouse Meltrin α monoclonal antibody which reacted with the peptide antigens. The results are shown in Table 5.

TABLE 5 Hybridomas producing anti-Meltrin peptides monoclonal antibody

Peptide antigens	Hybridoma No.	The number of Hb
ProA	F936	10
MP-B	F939	4
DC-C	F933	4
DEA	F934	8

[0177] Purified antibodies were obtained from the thus established anti-Meltrin monoclonal antibody-producing hybridoma cell lines by the following method.

[0178] The hybridomas were cultured in RPMI1640 supplemented with 10% fetal bovine serum and 1ng/ml of human IL6 till a final density of 2 x 10^5 cells/ml. The medium was then exchanged with a serum-free medium (Hybridoma-SFM, GIBCO BRL), and the culture was continued until the cells died. The resulting culture supernatant was filtered through filter paper for the removal of the cells, and subjected to purification by Protein G column (Prosep-G, Bioprocessing INC) as follows. The culture supernatant (1L) was applied to Prosep-G column (20ml) at a flow rate of 10ml/min, followed by washing with 0.1M phosphate buffer (pH 7.5) comprising 0.15M NaCl. After the absorbance at 280nm had decreased, the bound monoclonal antibody was eluted by 0.1M citric acid buffer (pH 3.0). After neutralization of the pH, the eluate was concentrated with DIAFLO (Grace Japan), and dialysed against 0.076M phosphate buffered saline (pH 6.4) comprising 0.45% NaCl. The concentration of the purified antibody was calculated on the basis of the absorbance at 280nm.

(6) Evaluation of monoconal antibody

[0179] The binding activity of 7 lots of the purified antibodies (10 μg/ml each) obtained in the above (5) to Meltrin was confirmed by Western blotting according to the method of the above (4) using the cell lysate of #9-3 cell. The results are shown in Fig. 19. The band of about 67kDa specific to the cell lysate of #9-3 cell was detected by the reaction with F933-4-3 (subclass IgG2a), F933-10-26 (subclass IgG2a), F934-17-6 (subclass IgG2a), F934-3-23 (subclass IgG2a), F934-4-33 (subclass IgG2a), F934-6-3 (subclass IgG2a), and F934-20-5 (subclass IgG2c). As these bands were not detected in the case of the cell lysate of L929 cell, it was confirmed that the monoclonal antibodies obtained in the above (5) were bound to Meltrin.

Example 11: Preparation of anti-mouse Meltrin monoclonal antibody

(1) Preparation of the antigen to be adminitered and immunization of rat

[0180] Rats were immunized with #9-3 and #3-5 cells as the antigen to be administered as follows. The cells used as the antigen to be administered were cultured in the absence of bFGF. First, the cells cultured in four dishes to a density of about 5 x 10^5 cells /ϕ 10cm dish were subcultured in 20 dishes to until the same density as the above, then again subcultured in 40 dishes (ϕ 15cm) up to a density of about 5 - 6 x 10^6 cells / dish, and futher cultured in a differentiation

medium (DMEM supplemented with 2% horse serum) for two days to finally form myotube. These cells were then scraped with a silicon rubber Policeman, washed two times with PBS, and suspended into the medium comprising 10% DMSO for storage at -80°C.

[0181] The #9-3 and #3-5 cells were suspended in physiological saline (200μl), mixed with an equiamount of Freund's complete adjuvant (DIFCO) and intraperitoneally administered into Wistar rat (5 weeks old, female) in an amount of 1 x 10^7 cells/rat. The antigen was mixed with the same amount of Freund's incomplete adjuvant (DIFCO) and administered two weeks later in the same way as above.

(2) Evaluation of antiserum

[0182] After one week from the boosting, the blood was drawn from the eyeground of the rat, and a binding of antiserum to Meltrin was determined by using the cell extract according to the plate assay of Example 10 (3). The cell extracts of #9-3, #3-5 and L929 cells were prepared according to the method of Example 10 (4), except that NP-40 (Nacarai Tesque Co.) was used at a final concentration of 0.5% as a surfactant.

[0183] First, each cell extract was dilulted with PBS to a concentration of 40 μg/ml, each 50μl of which was separately poured into each well of an immuno plate (Maxisorp Nunc). After incubation at 56°C for 30min for binding of the antigen, the wells were washed five times with ion-exchanged water, blocked by 20 % Block Ace (Yukijirushi Milk Co.) / PBS 100μl, followed by incubation at a room temperature for 30min. After removal of the blocking agent, each antiserum (50μl) was added and incubated at 37°C for one hour. After two repeats of washing of the wells with the washing liquid, 50μl of an anti-rat immunoglobulins antibody labelled with peroxidase (Dako) and diluted 1,000 times with 10% Block Ace /PBS was added to each well followed by incubation at 37°C for one hour. Upon the completion of the reaction, the wells were washed five times with the washing liquid and two times with ion-exchanged water, and 50μl of 0.1M McIlvaine buffer (pH 5.0) comprising 3mg/ml of o-phenylene diamine and 0.027% hydro peroxide was added and reacted for 10 min. The reaction was terminated by the addition of 1N HCl (50 μl), and the absorbance at 490 nm was measured.

[0184] Western blotting was also carried out by using the cell extract of L4-3 described in the following (4) to confirm its binding to Meltrin. The results are shown in Table 6.

[0185] It was confirmed that the antiserum obtained from the rats immunized with #9-3 and #3-5 cells reacted with the corresponding cell extract, and were bound to Meltrin in the Western blotting.

TABLE 6 Reaction of antiserum of the rats immunized with #9-3 and #3-5 cells to Meltrin

Antiserum	Plate Assay			Western blotting
	#9-3	#3-5	L929	L4-3
rat immunized with #9-3 cell	+	N.D.	-	+
rat immunized with #3-5 cell	N.D.	+	-	+

N.D. (not determined)

(3) Preparation of monoclonal antibody

[0186] The #9-3 and #3-5 cells (1 x 10^7 cells each) were suspended in physiological saline (200μl), and intraperitoneally administered into the rat whose antibody titer had increased. Three days later, cell fusion was carried out by using myeloma P3X63Ag8U.1 according to the known method (Monoclonal antibody Jikken Sosa Nyumon (Guide of monoclonal antibody preparation), Tamie Ando and Jo Chiba, Koudan-sha Scientific). Six days later, the culture supernatant was screened by its reactivity with the immobilized cell extracts. The wells that showed reactivity with the cell extracts were subjected to cloning by limiting dilution (Monoclonal antibody Jikken Sosa Nyumon (Guide of monoclonal antibody preparation), Tamie Ando and Jo Chiba, Koudan-sha Scientific). After cloning, the above screening was repeated to give 13 clones, 5 clone from the rat immunized with #9-3 (δPro; hybridoma No. F932) and 8 clones from the rat immunized with #3-5 (δMP; hybridoma No. F937).

(4) Evaluation of monoconal antibody

[0187] The monoclonal antibodies F932-15-2 (subclass IgG1) and F937-9-2 (subclass IgG1) that showed a high reactivity with the cell extracts were evaluated.

[0188] First, the staining of myotube formed by C2 cells was examined by a cell immunofluorescence staining method. C2 cells were suspended in 10% FCS/DMEM at a density of 3 x 10^4 cells/ml, each 100μl of which was then separately poured into the wells of chamber slide (Lab-TEK, Nunc Co.). After the culture at 37°C and 5% CO_2 for two days, the medium was exchanged with 2% horse serum/DMEM. The cell staining was carried out by using myotube formed two

days later. The cells were washed two times with PBS$^-$, and 4% formaldehyde was added followed by the reaction at a room temperature for 30min to fix the cells. The cells were washed three times with PBS$^-$ and blocked with 20% Block Ace /T-PBS. After removal of the blocking agent, antibodies diluted to 10μg/ml with 20% Block Ace /T-PBS was added and reacted at a room temperature for one hour. After three repeats of washing of the wells with PBS$^-$, an anti-rat immunoglobulins antibody FITC (Dako) diluted 20 times with 10% rabbit serum/T-PBS was added to each well followed by incubation a room temperature for one hour. After the completion of the incubation, the cells were washed three times with PBS$^-$, and subjected to fluorescence microscopy. It was observed that myotube was stained by both the antibodies, but not stained by rat IgG (ZYMED) used as a negative control.

[0189] Next, L929 cells experssing mouse Meltrin α or β were prepared and subjected to cell staining for the purpose of confirmation of the specificity of the above antibodies. Thus, fibroblast L929 was transfected with the mixture comprising the plasmids pBOSMelα(+) and pBOSMelβ(+) prepared in Example 4, and the plasmid pSV2NEO in a molar ratio of 12:12:1 by using LIPOFECTAMINE (Gibco BRL) according to its protocol to give L4-3 cells expressing mouse Meltrins α and β. Similarly, 1929 was transfected with the mixture comprising the plasmids pBOSMelβ(+) and the plasmid pSV2NEO in a molar ratio of 20:1 to give L2-10 cells expressing mouse Meltrin β. Similarly, L929 was transfected with the plasmids pBOSMelαδPro(+) to give L8-5 cells expressing mouse Meltrin α δPro. The transfected cells were cultured in 10% FCS/DMEM and subcultured onto a chamber slide. The specificity of the antibodies was confirmed by cell staining using L929, L4-3, L2-10 and L8-5 cells. The results shown in Table 7 indicated that F932-15-2 was bound to Meltrins α and β, and F937-9-2 was bound to Meltrin α.

[0190] The hybridoma expressing the monoclonal antibody F932-15-2 was deposited with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on October 3, 1996 under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5687.

TABLE 7

Cell	Expression	F932-15-2	F937-9-2
L929	-	-	-
L4-3	α and β	+	+
L2-10	β	+	-
L8-5	α (δPro)	+	+

(5) Determination of neutralizing activity

[0191] The neutralizing activity of the monoclonal antibodies obtained in the above (3) was confirmed by their inhibition of the formation of myotube by C2 cells. C2 cells were cultured in a collagen-coated dish contianing 10% FCS/DMEM till 80% of confluence, followed by exchange of the medium with 2% horse serum/DMEM supplemented with 0 or 40μg/ml of the antibodies to be tested. The formation of byotube was then observed and the ratio of nuclei in the formed myotube was calculated. As seen from Fig.20, the formation of myotube on the day 2 was inhibited, showing that both F932-15-2 and F937-9-2 have the neutralizing activity.

Example 12: The activity of Meltrin neutralizing antibodies to inhibit the formation of bone resorption area (pit) in mouse unfractionated bone cells

[0192] Femur and tibia extracted from 13-day-old ICR mouse were crushed in MEM α medium (GIBCO) supplemented with 5% FBS. After being allowed to stand still for 2min, the precipitaed bone residues were removed. The supernatant of the suspending cells was adjusted to 1 x 10^7 cells/ml, 100μl of which was then added to each well of a 96 well microplate provided with ivory fragments. The ivory fragments had been thinly sliced, punched into 6mm in diameter, washed with 70% ethanol and sterilized. The mouse Meltrin-neutralizing antibody (F932-15-2) obtained in Example 11, and rat IgG were diluted with MEM α medium (GIBCO) supplemented with 5 % FBS to final concentrations of 5, 50, and 500μg/ml, 100μl of which was then added to each well. After incubation at 37°C and 5% CO_2 for three days, the cells were removed with a scraper, and resorption area was stained with an acid hematoxylin solution (SIGMA) for about 7min and the number of the stained resorption area was caluculated using an ocular micrometer under a microscope by counting the number of squares wherein resorption fossa was contained.

[0193] The results are shown in Fig. 21, which demonstrates that the number of the formed resorption area was inhibited in a dose-depending manner by the mouse Meltrin-neutralizing antibody. Accordingly, it was suggested that the Meltrin-neutralizing antibody would affect directly or indirectly osteoclast and inhibit bone resorption.

Example 13: Serum Ca-decreasing activity of Meltrin-neutralizing antibody in mouse having enhanced bone resorption

[0194] Seven-week-old ICR mice (male) were fed for five days with low Ca feed with Ca content of 0.02% or less. The mouse Meltrin-neutralizing antibody (F932-15-2) obtained in Example 11 was injected into the tail vein of the mice (one group consisting of five mice) at doses of 0.1mg and 1mg per mouse). Rat IgG (Img per mouse) and phosphate buffer physiological saline were also injected as a control in the same way. Before injection and one day later, the blood was collected from the vein under eyes, and serum was separated. The value of Ca in the serum was then determined by an autoanalyzer (COBAS FARAII, ROCHE) using Ca determination kit (CalciumHR-II, WAKO Pure Pharmaceuticals). The results are shown in Fig.22.

[0195] As seen from Fig.22, the serum Ca value after one day from the injection in the groups treated with the mouse Meltrin-neutralizing antibody was lower than that of the groups treated with rat IgG or physiological saline. These results suggested that the Meltrin-neutralizing antibody would inhibit an unhealthly enhanced bone resorption due to hyperparathyroidism or malignant hypercalcemia.

Example 14: Preparation of cDNA fragment encoding human Meltrin α comprising transmembrane domain

[0196] A sense primer S-hMelα-TM5'was synthesized based on the partial cDNA sequence of human Meltrin α obtained in Example 8, and an antisense primer A-mMelα-3' was synthersized based on the cDNA sequence of mouse Meltrin α (see Table 1).

[0197] PCR was carried out by mixing the human placenta λgt11 cDNA library (Clonetech Co., code No. CLHL1008b) as a template, with S-hMelα-TM5' and A-mMelα-3' primers, Ex Taq polymerase (TaKaRa Co.,), and its reagents (TaKaRa Co.,), followed by 35 cycles of the reactions at 94°C for 30sec, 55°C for 30sec, and 72°C for one min. The base sequencing of the resulting amplified fragment (clone TM) suggested that the fragment was a human cDNA fragment corresponding to about 220 amino acids comprising the transmembrane domain of mouse Meltrin.

[0198] The obtained base sequence and its corresponding amino acid sequence are shown in Fig.23a - Fig.23b.

Example 15: Acute toxicity test

[0199] The mouse Meltrin-neutralizing antibody (F932-15-2) obtained in Example 11 was injected into seven-week-old ICR male mice (one group consisting of five mice) at doses of 1mg and 3mg per mouse). Phosphate buffer physiological saline was also injected into a control group in the same way. Neither significant decrease of body weight nor side effect was observed in any group after the injection. No dead mouse was observed, either.

Reference Example 1: Preparation of monoclonal antibody recognizing human Meltrin

(1) Preparation of antibody using a peptide having the amino acid sequence derived from human Meltrin as an antigen

[0200] In consideration of the results obtained in Example 10, the sequence "GKVSKSSFAKCEMRDAKC" corresponding to DC-C in the amino acid sequence of human Meltrin α obtained in Example 8 was synthesized in the same way as in Example 10 (1), purified and conjugated with maleimidated KLH to give an antigen to be administered. 20μg of the antigen was dissolved in 0.1ml of physiological saline and mixed with an equiamount of FCA followed by injection to ddy mouse (5 weeks old, female). The same amount of the antigen was mixed with FIA and injected two weeks later. The blood was collected from the eyeground one week later and antiserum was prepared. Evaluation of the reactivity of the resulting antiserum with the administered peptide according to the method of Example 10 (3) revealed its specific reactivity with the administered peptide. Accordingly, mouse, rat, hamster and the like are immunized with the peptide antigen, and monoclonal antibody may be prepared in the same manner as in Example 10 (5). Such antibody may also be used in Western blotting.

[0201] As it is estimated that the amino acid sequence in Fig.15a - Fig.15f is Meltrin α of a soluble type, an antibody, which may be effectively used in the determination of soluble Meltrin in the body, may be prepared by immunization of a peptide having the amino acid sequence adjacent to C-termial of the above sequence.

[0202] Similarly, antibodies recognizing human Meltrin β and Meltrin γ may be prepared by chemically synthesizing peptides having the amino acid sequences of suitable parts in the amino acid sequences in Fig.17a - Fig.17c or Fig.13a - Fig.13d and injecting the thus synthesized peptides into animals. In any case, the amino acid sequence will be selected from the extracellular domain.

[0203] For the preparation of an antibody specific to each one of Meltrins α, β and γ, the amino acid sequence should be selected from the parts with a low homology among them, and a peptide having the thus selected amino acid sequence is synthesized and injected to animals such as mouse, rat and hamster in the same way as in Example 10 (2).

[0204] In any case, monoclonal antibodies are prepared in the same way as in Example 10 (5).

(2) Preparation of anti-Meltrin monoclonal antibody using cells expressing human Meltrin as an antigen

[0205] DNA encoding the amino acid sequence wherein the amino acid sequence located downstream of the transmembrane domain shown in Fig.23a - Fig.23b is fused downstream of the sequence from the metalloproteinase or the disintegrin domain to the cysteine-rich region shown in Fig. 15a- Fig. 15f is prepared, and inserted into an expression vector pEFBOS, followed by transformation of C2 cells by the resulting vector. The transformant is treated as in Example 11 (1), and used as an antigen for immunization of animals such as mouse, rat and hamster. Antibodies recognizing human Meltrin α is screened as in Example 11 (2), and monoclonal antibodies are prepared as in Example 11 (3).

[0206] Similarly, DNA encoding the amino acid sequence shown in Fig.17a - Fig-17c or the sequence located downstream of the disintegrin domain of the above sequence is prepared, and inserted into an expression vector pEFBOS, followed by transformation of C2 cells by the resulting vector. The transformant is treated as in Example 11 (1), and used as an antigen for immunization of animals such as mouse, rat and hamster. Antibodies recognizing human Meltrin β is screened as in Example 11 (2), and monoclonal antibodies are prepared as in Example 11 (3).

[0207] Similarly, DNA encoding the amino acid sequence shown in Fig.13a - Fig.13d or the sequence located downstream of the disintegrin domain of the above sequence is prepared, and inserted into an expression vector pEFBOS, followed by transformation of C2 cells by the resulting vector. The transformant is treated as in Example 11 (1), and used as an antigen for immunization of animals such as mouse, rat and hamster. Antibodies recognizing human Meltrin γ is screened as in Example 11 (2), and monoclonal antibodies are prepared as in Example 11 (3).

SEQUENCE LISTING

[0208]

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: MOCHIDA PHARMACEUTICAL CO., LTD.
(B) STREET: 7, Yotsuya 1-chome, Shinjuku-ku
(C) CITY: Tokyo
(E) COUNTRY: Japan
(F) POSTAL CODE (ZIP): 160

(ii) TITLE OF INVENTION: MELTRINS

(iii) NUMBER OF SEQUENCES: 28

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(v) CURRENT APPLICATION DATA:

APPLICATION NUMBER: EP 96935358.0

SEQ ID NO:1

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6915 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE: JM109(pBSMel α)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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GCCAGAGTAG CGCGCGCGCG CACGCACACA CACGGGGAGG GGAGAAAGTT TTTTTTTGAA     60
AAAATGAAAG GCTAGACTCG CTGCTCAGCG ACCCGGGCGC TGCGCGAGGG GGTCGCGGCA    120
GACTCAGGGC AGTAGGACTT CCCCCAGCTC GGCGCCCGCG TGGGATGCTG CAGCGCTGGC    180
CGCGGGGCCC CCGAAGCAGC TGCACGCCAG GCCGGCGACA ATG GCA GAG CGC CCG       235
                                              Met Ala Glu Arg Pro

GCG CGG CGC GCG CCC CCC GCC CGC GCC CTC CTG CTG GCC CTG GCT GGG       283
Ala Arg Arg Ala Pro Pro Ala Arg Ala Leu Leu Leu Ala Leu Ala Gly

GCC CTG CTG GCG CCC CGT GCA GCC CGA GGG ATG AGT TTG TGG GAC CAG      331
Ala Leu Leu Ala Pro Arg Ala Ala Arg Gly Met Ser Leu Trp Asp Gln

AGA GGA GCT TAC GAA GTG GCC AGA GCC TCC CTT CTG AGC AAG GAC CCT      379
Arg Gly Ala Tyr Glu Val Ala Arg Ala Ser Leu Leu Ser Lys Asp Pro

GGG ATC CCA GGA CAG AGC ATC CCA GCC AAG GAT CAT CCA GAC GTG CTG      427
Gly Ile Pro Gly Gln Ser Ile Pro Ala Lys Asp His Pro Asp Val Leu
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ACT GTG CAA CTG CAG CTG GAG AGC CGA GAC CTG ATC CTC AGC CTG GAA      475
Thr Val Gln Leu Gln Leu Glu Ser Arg Asp Leu Ile Leu Ser Leu Glu

AGG AAT GAG GGA CTC ATT GCC AAT GGC TTC ACG GAG ACC CAT TAT CTG      523
Arg Asn Glu Gly Leu Ile Ala Asn Gly Phe Thr Glu Thr His Tyr Leu

CAA GAT GGT ACT GAT GTC TCT CTC ACT CGA AAT CAC ACG GAT CAT TGT      571
Gln Asp Gly Thr Asp Val Ser Leu Thr Arg Asn His Thr Asp His Cys

TAC TAC CAT GGA CAT GTG CAA GGA GAT GCT GCA TCA GTG GTC AGC CTC      619
Tyr Tyr His Gly His Val Gln Gly Asp Ala Ala Ser Val Val Ser Leu

AGT ACT TGC TCT GAT CTC CGG GGA CTT ATC ATG TTT GAA AAT AAA ACG      667
Ser Thr Cys Ser Asp Leu Arg Gly Leu Ile Met Phe Glu Asn Lys Thr

TAC AGC TTA GAG CCA ATG AAA AAC ACC ACT GAC AGC TAC AAA CTC GTC      715
Tyr Ser Leu Glu Pro Met Lys Asn Thr Thr Asp Ser Tyr Lys Leu Val

CCA GCT GAG AGC ATG ACG AAC ATC CAA GGG CTG TGT GGG TCA CAG CAT      763
Pro Ala Glu Ser Met Thr Asn Ile Gln Gly Leu Cys Gly Ser Gln His

AAC AAG TCC AAC CTC ACC ATG GAA GAT GTC TCC CCT GGA ACC TCT CAA      811
Asn Lys Ser Asn Leu Thr Met Glu Asp Val Ser Pro Gly Thr Ser Gln

ATG CGG GCA AGA AGG CAT AAG AGA GAG ACC CTT AAG ATG ACC AAG TAC      859
Met Arg Ala Arg Arg His Lys Arg Glu Thr Leu Lys Met Thr Lys Tyr

GTA GAG CTG GTT ATT GTG GCA GAC AAC AGA GAG TTT CAG AGG CAA GGA      907
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Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile Ala Asn His

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Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val Leu Val Gly

GTG GAA GTG TGG AAT GAC ATC GAC AAA TGC TCT ATA AGC CAG GAC CCA     1051
Val Glu Val Trp Asn Asp Ile Asp Lys Cys Ser Ile Ser Gln Asp Pro

TTC ACC AGG CTC CAT GAG TTT CTA GAC TGG AGA AAG ATA AAG CTT CTA     1099
Phe Thr Arg Leu His Glu Phe Leu Asp Trp Arg Lys Ile Lys Leu Leu

CCT CGA AAA TCC CAC GAC AAT GCT CAG CTT ATC AGT GGG GTT TAT TTC     1147
Pro Arg Lys Ser His Asp Asn Ala Gln Leu Ile Ser Gly Val Tyr Phe

CAA GGA ACC ACC ATC GGC ATG GCA CCC ATC ATG AGC ATG TGC ACT GCA     1195
Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met Cys Thr Ala

GAA CAG TCT GGA GGA GTT GTC ATG GAC CAT TCA GAC AGC CCC CTT GGT     1243
Glu Gln Ser Gly Gly Val Val Met Asp His Ser Asp Ser Pro Leu Gly

GCC GCA GTG ACC TTG GCA CAT GAG CTG GGC CAC AAC TTC GGG ATG AAC     1291
Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe Gly Met Asn

CAT GAC ACA CTG GAG AGG GGC TGC AGC TGC AGA ATG GCC GCA GAG AAA     1339
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His Asp Thr Leu Glu Arg Gly Cys Ser Cys Arg Met Ala Ala Glu Lys

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Gly Gly Cys Ile Met Asn Pro Ser Thr Gly Phe Pro Phe Pro Met Val

TTC AGC AGC TGC AGC AGG AAG GAC CTG GAG GCT AGC CTG GAG AAG GGC     1435
Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Ala Ser Leu Glu Lys Gly

ATG GGG ATG TGC CTC TTC AAC CTA CCA GAG GTC AAG CAG GCC TTT GGG     1483
Met Gly Met Cys Leu Phe Asn Leu Pro Glu Val Lys Gln Ala Phe Gly

GGC CGG AAG TGT GGA AAT GGC TAT GTG GAA GAG GGA GAA GAG TGT GAC     1531
Gly Arg Lys Cys Gly Asn Gly Tyr Val Glu Glu Gly Glu Glu Cys Asp

TGC GGA GAA CCG GAG GAA TGC ACG AAT CGC TGC TGT AAC GCT ACC ACC     1579
Cys Gly Glu Pro Glu Glu Cys Thr Asn Arg Cys Cys Asn Ala Thr Thr

TGT ACT CTG AAG CCA GAT GCT GTG TGC GCG CAC GGG CAG TGC TGT GAA     1627
Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly Gln Cys Cys Glu

GAC TGT CAG CTG AAG CCT CCA GGA ACT GCA TGC AGG GGC TCC AGC AAC     1675
Asp Cys Gln Leu Lys Pro Pro Gly Thr Ala Cys Arg Gly Ser Ser Asn

TCC TGT GAC CTC CCA GAA TTC TGC ACA GGG ACT GCC CCT CAC TGT CCA     1723
Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Thr Ala Pro His Cys Pro

GCC AAT GTG TAC CTA CAT GAT GGC CAC CCG TGT CAG GGC GTG GAT GGT     1771
Ala Asn Val Tyr Leu His Asp Gly His Pro Cys Gln Gly Val Asp Gly

TAC TGC TAC AAC GGC ATC TGC CAG ACC CAT GAG CAG CAG TGT GTC ACG     1819
Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln Gln Cys Val Thr

CTC TGG GGA CCA GGT GCT AAA CCG GCT CCT GGC ATC TGC TTT GAG CGA     1867
Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg

GTC AAC TCT GCA GGA GAT CCT TAT GGT AAC TGT GGC AAA GAC TCC AAG     1915
Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly Lys Asp Ser Lys

AGC GCC TTC GCC AAA TGT GAG CTG AGA GAT GCC AAG TGT GGG AAA ATC     1963
Ser Ala Phe Ala Lys Cys Glu Leu Arg Asp Ala Lys Cys Gly Lys Ile

CAG TGT CAA GGT GGT GCA AGC CGA CCT GTC ATT GGT ACC AAT GCT GTT     2011
Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly Thr Asn Ala Val

TCC ATA GAA ACA AAT ATC CCA CAG CAG GAA GGA GGT CGG ATT CTG TGC     2059
Ser Ile Glu Thr Asn Ile Pro Gln Gln Glu Gly Gly Arg Ile Leu Cys

CGG GGG ACC CAT GTG TAC TTG GGT GAT GAC ATG CCA GAC CCA GGG CTT     2107
Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro Asp Pro Gly Leu

GTG CTT GCA GGA ACA AAG TGT GCA GAA GGA AAA ATC TGC CTC AAT CGT     2155
Val Leu Ala Gly Thr Lys Cys Ala Glu Gly Lys Ile Cys Leu Asn Arg

CGA TGT CAG AAT ATC AGT GTC TTC GGC GTT CAC AAG TGT GCC ATG CAG     2203
Arg Cys Gln Asn Ile Ser Val Phe Gly Val His Lys Cys Ala Met Gln
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TGC CAC GGC CGA GGG GTA TGT AAC AAC AGG AAG AAT TGC CAC TGT GAA      2251
Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn Cys His Cys Glu

GCC CAC TGG GCT CCA CCC TTC TGT GAC AAG TTT GGC TTT GGA GGA AGC      2299
Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly Phe Gly Gly Ser

ACA GAC AGT GGT CCC ATC AGG CAA GCA GAT AAC CAG GGC TTG ACT GTA      2347
Thr Asp Ser Gly Pro Ile Arg Gln Ala Asp Asn Gln Gly Leu Thr Val

GGA ATC CTG GTG AGC ATC CTG TGT CTG CTT GCT GCT GGA TTT GTG GTG      2395
Gly Ile Leu Val Ser Ile Leu Cys Leu Leu Ala Ala Gly Phe Val Val

TAT CTC AAA AGG AAG ACG TTG ATG CGG CTG CTG TTC ACA CAT AAA AAA      2443
Tyr Leu Lys Arg Lys Thr Leu Met Arg Leu Leu Phe Thr His Lys Lys

ACC ACC ATG GAA AAG CTA AGG TGT GTG CAC CCT TCC CGG ACA CCC AGT      2491
Thr Thr Met Glu Lys Leu Arg Cys Val His Pro Ser Arg Thr Pro Ser

GGC CCT CAC CTT GGC CAG GCT CAC CAC ACC CCC GGG AAA GGC CTG CTG      2539
Gly Pro His Leu Gly Gln Ala His His Thr Pro Gly Lys Gly Leu Leu

ATG AAC CGG GCA CCA CAT TTC AAT ACC CCC AAG GAC AGG CAC TCG CTG      2587
Met Asn Arg Ala Pro His Phe Asn Thr Pro Lys Asp Arg His Ser Leu

AAA TGC CAG AAC ATG GAC ATC AGC AGG CCC CTC GAC GCT CGA GCC GTC      2635
Lys Cys Gln Asn Met Asp Ile Ser Arg Pro Leu Asp Ala Arg Ala Val

CCA CAG CTT CAG TCA CCT CAG CGA GTG CTC CTG CCT CTC CAC CAG ACC      2683
Pro Gln Leu Gln Ser Pro Gln Arg Val Leu Leu Pro Leu His Gln Thr

CCA CGT GCA CCC AGT GGC CCT GCC AGG CCC CTG CCC GCC AGT CCT GCA      2731
Pro Arg Ala Pro Ser Gly Pro Ala Arg Pro Leu Pro Ala Ser Pro Ala

GTC AGG CAG GCC CAG GGC ATT CGA AAA CCC AGT CCT CCT CAG AAG CCT      2779
Val Arg Gln Ala Gln Gly Ile Arg Lys Pro Ser Pro Pro Gln Lys Pro

CTG CCT GCT GAT CCA CTG AGC AGG ACT TCT CGG CTC ACT AGT GCC TTG      2827
Leu Pro Ala Asp Pro Leu Ser Arg Thr Ser Arg Leu Thr Ser Ala Leu

GTG AGG ACC CCA GGG CAG CAG GAA CCT GGG CAC CGC CCA GCC CCC ATC      2875
Val Arg Thr Pro Gly Gln Gln Glu Pro Gly His Arg Pro Ala Pro Ile

AGA CCT GCC CCT AAG CAT CAA GTA CCC AGA CCT TCC CAC AAT GCC TAT      2923
Arg Pro Ala Pro Lys His Gln Val Pro Arg Pro Ser His Asn Ala Tyr

ATC AAG TGAGAAGCCA GCCCAGACCG GTCCTCAACA GTGAAGACAG AAGTTTGCAC      2979
Ile Lys

TATCTTCAGC TCCATTGGAG TTGTTGTTGT ACCAACTTTC CGAGTTTCTA AAGTGTTTAA   3039
AACACCATTC TCTCCAGACC CTGGAGCCAC TGCCATCGGT GCTGTGCTGT GGTGCTTTGT   3099
GTACTTGCTC AGGAACTTGT AAGTTATTAA TTTATGCAGA GTGTCTATTA CTGCGCAGGG   3159
CGCCGTAGCA GGCATTTGTA CCATCACAGG GCTTTTCTAC AGAAGGAAGG CTCCTCGTGC   3219
TTTTGTTTTT CTGGAGGACT TGAAATACCC TGCTTGATGG GACCTAAGAT GAGATGTTTA   3279
CTTTCTATTC AAGGCCTTAT CGGAAAATAG CTCCCCACCT TCCCAAGGCT GTTATGGTAC   3339
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CAGACACACA GCTCAGGACA CCCCAGGGAG AACCTGGCAT GGGTTTTCTT TGTTTGCTTT  3399
CATTTTATCT TTTATATTTT GGTATCCCTA TCTTGGGTTG TAGCCAGGGC CTTCAGGAAG  3459
GTCTTGGGCC ACTGCATGCT AATGGCCTTC AGGTCCTGCA CCCTGAAGCT CTCAGACAAC  3519
AAGTAGGATC TGCTTTCTAG CCAGCAGCTT TGGAGAGAAC CTGGGGTACT GAAAAGAAGG  3579
TTTGGGGTGT GGTTATACCA GGATGGAGAC TGGAATCCTA ATCTGGGCAA ACATCTGACC  3639
TTGAGCTGAG CAGCCATGAG CACCTCTAGG AAGCAAGGAC GGCTGAGGTG CTGCACAAGG  3699
CTCTGCTTTG AGAGCTGGCA GGGGCTTCTC TCTGGCTGCC CTTTGCAGAG TGCTAGCTGG  3759
CATGGCATGT TGTTTACATC GGGAACAGTG GTGTTTCTAC AAGAAAGCCA CTGCCTGGGC  3819
ACTGCAGACC TCCGTCTCCT GCCCATTTAG AGCTAAGCAA ATTACCACAT TGTCTTCTGG  3879
ACTGTAATAC AATGACCCTG TGTTCTGACA GATAGAGGAG GCTTTCTATG GAACCATAAC  3939
TATTTTCANA TGTGAACTAG TAACCAGATC TAGTCGATCA ACTCTGGAGA TAGAAATCTC  3999
CTTTTTACTG CAAGGCTCGA CTTATTAAAA ATTAGGCAGA ATCCATATGC TTGCAAAAGC  4059
TATAACCACG TGGAATGCTC TTCTCATGGC ACAGCCTGAG TCTGGTATCC TTATTAGTAG  4119
CCATTGGACA AAGCACCCAA AGTTACCTGT GTGTTCTCTT CAAGGCATCC TAATTTCTTC  4179
AGCATAGAGA GACTCGGTCT TCCTCACATT CTGAACATAC CTATCAATGA CTAAGNCAGC  4239
AAGGCAATCC GTTTCCGAAT ACTGAGTTGC TCACGGNAAG GCAACCTCAG CCCAGGNAAA  4299
CTTTTTTCCT CTGNTCTTTC AGTATGTGAC TGGGGAGCTA CCTTCAGAAG CAAATTTTCA  4359
AGGTGGNCTC AACCCCATNG GATGAAAGNT ATTTTTTTAA AAAATAATTA ATGGTAATGC  4419
CAGAGGGCTT TCCTGGCNTC CAGATNGGGG CGTAGGNTTG ACTAGCTTTC ACGACAGAAG  4479
GTAAATGACA GCAGTCCTCT ACCTCGTCTG ACTGCTTTAA GATCAAGGCT TCTTTGGAAG  4539
GGTAACTAAC ATTAATGGCT GGCCTGTGCC TTGAAGCAGA AGGGAAAATA CAGATAAGGA  4599
ATTTGGTTTG CTTTCTAGAA TCCAAAACTG TATCCAGCAT TGGGAAGCAT GGTCTTCATG  4659
ACTGGGTAAA TAAATCCACG TCACAGATGC ATAAAAGAAT AACTCTTATG ACATGCCTCT  4719
TTTTGTGGCA CAGAGACAAT ATTGCTGCCA CTGAGATGCA TACAAAATTT CTGTAACTGA  4779
TATGTCATTC AGTAGTTGTA TTAAGGCCAA ACATCCACAA CTGTAAAGAC TTATAGAGTT  4839
GTGTGGGCGT TGTCTTGTGA GACACACAAA GCCTCAGCTG AAGCGTATGA GCTCCTCCTC  4899
CAGGTGGGAG TGATGGGGAG GCTAGAAACA CACAAAGACA ACAGAAGAGC TTTGGTTTGG  4959
GGGGGGTGCA GAGAGAGTGT GGTTTAGAGG AAGTTGGAGC CATGATCTTC TGCCATCTCC  5019
CCAGTGTCCA CTAAGGATGC CGATGGTGCC TTACCAGCTG TGCAGTGCTG GCTGCTTGCT  5079
TTTACAGAGC CATGCATTCA TTTCTGAATA AGAACATATT TAATCCTGAA ATTCCCTTAC  5139
AGGACAGACA GTGTTACTAA AGGAATTCCT CTAAGATACA GTAGTTGTCA ATTAAAGCAT  5199
ATTTAGCAGT AACTTCAATT TTAACAAAAT TGGGACCCAA TAGCCAGCAT GAGGGTTCTT  5259
TGACAGAGGG TAGTTTCTCT CTCCCTTTCT CCATCCTTCA AATGACAAGA CGTCAAAACT  5319
AATACAGTTC ATTTGCAGTC CATCTCATGC TTATACATAC TAGAGGTATG ACTAAAGTTG  5379
GTTGAGTCAT GGGAGACCAT CCCTGAGAAA GTCCAGTCGG TCAAGAGCCT TGCCAGGTGG  5439
CGTGGCTGGA CGTCCTCCTT TTGTTCCTGC ACTGAGGAAT AGTTATAGGT TATGTGACCC  5499
CACTTCACAG GCAAGTGGGA GGCGAACCTT GCAGGCATGC CCCTTAAAAG CTGGTCTCAG  5559
ACCTACAATA GTCCTGAGTC TGTTTTCCCA GCACACAGAG AGCAACAATG CAGTTTTCCA  5619
TTTCAAAATA TGCATGCCGA GTTTGCGCTC TGTGTGAGTG TTTCCAGGTT ACACATATGG  5679
GATGACATCA CAGAAACCAC ACAAGCAACA AATTAAATTC TACGGGAAGA AATCCTCCTG  5739
ACTGGTCTCT GAGGAGACAT TTTTATGCCT TCTTAACTTT ATTAGGAACT CTCAGGCTGA  5799
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CTGCCAAACC CTGATCTGTG TGAATGTTCT CAGGAGCCTG TGATCCCCAT GGTGCTANAA  5919
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GTCAGGCCCC AANCAGNGGA CACTGTCCTA TAGACCTCCC TCTNAGTTTT CAGACGGCCT  6159
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CTCCTGCCAA TCACAAGTGC CTTACTCTGA CCAGACCCAT GACAAAACCT CTGTCATCCA  6459
AGAGAGCCAA CTCTCTACCT TTGTTACTAC TTCAAGCCAA TGTGGTAACT GCTAACCTTC  6519
AAGGGTCACC TAAACAGTAT AGTCCAACCT TCACCAGGAC CATAGCACAG AGCAACCTCC  6579
AGNACACACA CACACACACA CCTTGAATCT ATCCCACAGC ATATCAACCC ACAGTGACCT  6639
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CCCTCCCACC GCCTTGTTCT AATTACAAGG TGAAGATGGC CATAGAAAAT CAAGTTAGCA   6699
CTAATTACAA AATGCTTTTG ATGCAACCTG AATTTCCCAA TGGCACCTAT TGCTTTGAAA   6759
CTCTGATGAG TTAAGTCATG CTCTGGGAGC TGTGAGCCCC ATGCTCAGAT CCACTGGGCA   6819
GGGGGGACTC CTTGCAGGAG ACATGGGCAC ACATATGAAT GTACCATTTC CATGCCTTTT   6879
GTGGAGTACA GACATATAAA CATAAATACT TCCATT                              6915
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SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 903 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ala Glu Arg Pro Ala Arg Arg Ala Pro Pro Ala Arg Ala Leu Leu

Leu Ala Leu Ala Gly Ala Leu Leu Ala Pro Arg Ala Ala Arg Gly Met

Ser Leu Trp Asp Gln Arg Gly Ala Tyr Glu Val Ala Arg Ala Ser Leu

Leu Ser Lys Asp Pro Gly Ile Pro Gly Gln Ser Ile Pro Ala Lys Asp

His Pro Asp Val Leu Thr Val Gln Leu Gln Leu Glu Ser Arg Asp Leu

Ile Leu Ser Leu Glu Arg Asn Glu Gly Leu Ile Ala Asn Gly Phe Thr

Glu Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Thr Arg Asn

His Thr Asp His Cys Tyr Tyr His Gly His Val Gln Gly Asp Ala Ala

Ser Val Val Ser Leu Ser Thr Cys Ser Asp Leu Arg Gly Leu Ile Met

Phe Glu Asn Lys Thr Tyr Ser Leu Glu Pro Met Lys Asn Thr Thr Asp

Ser Tyr Lys Leu Val Pro Ala Glu Ser Met Thr Asn Ile Gln Gly Leu

Cys Gly Ser Gln His Asn Lys Ser Asn Leu Thr Met Glu Asp Val Ser

Pro Gly Thr Ser Gln Met Arg Ala Arg Arg His Lys Arg Glu Thr Leu
-1 1

Lys Met Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu

Phe Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile

Glu Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg

Ile Val Leu Val Gly Val Glu Val Trp Asn Asp Ile Asp Lys Cys Ser

Ile Ser Gln Asp Pro Phe Thr Arg Leu His Glu Phe Leu Asp Trp Arg

Lys Ile Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Ile

Ser Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met
Ser Met Cys Thr Ala Glu Gln Ser Gly Gly Val Val Met Asp His Ser
Asp Ser Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His
Asn Phe Gly Met Asn His Asp Thr Leu Glu Arg Gly Cys Ser Cys Arg
Met Ala Ala Glu Lys Gly Gly Cys Ile Met Asn Pro Ser Thr Gly Phe
Pro Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Ala
Ser Leu Glu Lys Gly Met Gly Met Cys Leu Phe Asn Leu Pro Glu Val
Lys Gln Ala Phe Gly Gly Arg Lys Cys Gly Asn Gly Tyr Val Glu Glu
Gly Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Thr Asn Arg Cys
Cys Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His
Gly Gln Cys Cys Glu Asp Cys Gln Leu Lys Pro Pro Gly Thr Ala Cys
Arg Gly Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Thr
Ala Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Pro Cys
Gln Gly Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu
Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly
Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys
Gly Lys Asp Ser Lys Ser Ala Phe Ala Lys Cys Glu Leu Arg Asp Ala
Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile
Gly Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Gln Gln Glu Gly
Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met
Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Glu Gly Lys
Ile Cys Leu Asn Arg Arg Cys Gln Asn Ile Ser Val Phe Gly Val His
Lys Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys
Asn Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe
Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Asp Asn
Gln Gly Leu Thr Val Gly Ile Leu Val Ser Ile Leu Cys Leu Leu Ala
Ala Gly Phe Val Val Tyr Leu Lys Arg Lys Thr Leu Met Arg Leu Leu
Phe Thr His Lys Lys Thr Thr Met Glu Lys Leu Arg Cys Val His Pro

Ser Arg Thr Pro Ser Gly Pro His Leu Gly Gln Ala His His Thr Pro

Gly Lys Gly Leu Leu Met Asn Arg Ala Pro His Phe Asn Thr Pro Lys

Asp Arg His Ser Leu Lys Cys Gln Asn Met Asp Ile Ser Arg Pro Leu

Asp Ala Arg Ala Val Pro Gln Leu Gln Ser Pro Gln Arg Val Leu Leu

Pro Leu His Gln Thr Pro Arg Ala Pro Ser Gly Pro Ala Arg Pro Leu

Pro Ala Ser Pro Ala Val Arg Gln Ala Gln Gly Ile Arg Lys Pro Ser

Pro Pro Gln Lys Pro Leu Pro Ala Asp Pro Leu Ser Arg Thr Ser Arg

Leu Thr Ser Ala Leu Val Arg Thr Pro Gly Gln Gln Glu Pro Gly His

Arg Pro Ala Pro Ile Arg Pro Ala Pro Lys His Gln Val Pro Arg Pro

Ser His Asn Ala Tyr Ile Lys
698

SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6345 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B)CLONE: JM109(pBSMel β)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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GGCCGGGGGC AGGCAATGGC AGGGGATGTG TGATTGCGGA CAGTGAGAGG GCCGTTGCTA     60

TC ATG CCC GGG CGC GCG GGC GTC GCC CGG TTC TGC TTG CTG GCT CTC        107
   Met Pro Gly Arg Ala Gly Val Ala Arg Phe Cys Leu Leu Ala Leu

GCT CTG CAG CTA CAT TGG CCG CTG GCG GCG TGC GAG CCG GGA TGG ACC      155
Ala Leu Gln Leu His Trp Pro Leu Ala Ala Cys Glu Pro Gly Trp Thr

ACA AGA GGA AGC CAA GAA GGT AGC CCT CCG CTA CAG CAT GAA CTC ATA      203
Thr Arg Gly Ser Gln Glu Gly Ser Pro Pro Leu Gln His Glu Leu Ile

ATA CCT CAG TGG CGG ACT TCA GAA AGC CCT GGG AGA GGA AAG CAT CCA      251
Ile Pro Gln Trp Arg Thr Ser Glu Ser Pro Gly Arg Gly Lys His Pro

CTC AGA GCA GAG CTC AGG GTC ATG GCT GAA GGG CGA GAG CTG ATC CTA      299
Leu Arg Ala Glu Leu Arg Val Met Ala Glu Gly Arg Glu Leu Ile Leu

GAC CTG GAG AAG AAC GAG CAC CTT TTT GCT CCA GCC TAC ACA GAA ACC      347
Asp Leu Glu Lys Asn Glu His Leu Phe Ala Pro Ala Tyr Thr Glu Thr
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TGC TAC ACT GCA AGT GGC AAT CCT CAA ACC AGC ACG CTG AAG TCT GAG      395
Cys Tyr Thr Ala Ser Gly Asn Pro Gln Thr Ser Thr Leu Lys Ser Glu

GAT CAC TGC TTT TAC CAC GGG ACT GTG AGG GAC GTG GAT GAG TCC AGT      443
Asp His Cys Phe Tyr His Gly Thr Val Arg Asp Val Asp Glu Ser Ser

GTC ACG CTC AGC ACC TGC CGG GGA ATT AGA GGA CTG ATT ATA GTG AGA      491
Val Thr Leu Ser Thr Cys Arg Gly Ile Arg Gly Leu Ile Ile Val Arg

AGT AAC CTC AGC TAC ATC ATC GAG CCC GTC CCT AAC AGC GAC AGC CAA      539
Ser Asn Leu Ser Tyr Ile Ile Glu Pro Val Pro Asn Ser Asp Ser Gln

CAC CGT ATT TAC AGA TCC GAA CAT CTC ACG CTG CCC CCG GGG AAC TGT      587
His Arg Ile Tyr Arg Ser Glu His Leu Thr Leu Pro Pro Gly Asn Cys

GGG TTC GAG CAC TCC GGG CCC ACC TCG AAG GAC TGG GCC CTT CAG TTT      635
Gly Phe Glu His Ser Gly Pro Thr Ser Lys Asp Trp Ala Leu Gln Phe

ACA CAT CAG ACC AAA AAG CAA CCT CGC AGA ATG AAA CGG GAA GAT CTA      683
Thr His Gln Thr Lys Lys Gln Pro Arg Arg Met Lys Arg Glu Asp Leu

CAC TCT ATG AAG TAC GTG GAG CTT TAC CTG GTG GCT GAT TAT GCA GAG      731
His Ser Met Lys Tyr Val Glu Leu Tyr Leu Val Ala Asp Tyr Ala Glu

TTT CAG AAG AAT CGA CAT GAC CAG GAT GCC ACC AAA CGC AAG CTC ATG      779
Phe Gln Lys Asn Arg His Asp Gln Asp Ala Thr Lys Arg Lys Leu Met

GAG ATT GCC AAC TAT GTT GAT AAG TTT TAC CGC TCC CTG AAC ATC CGA      827
Glu Ile Ala Asn Tyr Val Asp Lys Phe Tyr Arg Ser Leu Asn Ile Arg

ATT GCA CTT GTC GGC TTG GAG GTG TGG ACG CAT GGG GAT AAG TGT GAA      875
Ile Ala Leu Val Gly Leu Glu Val Trp Thr His Gly Asp Lys Cys Glu

GTT TCA GAG AAT CCC TAC TCT ACC CTC TGG TCC TTT CTT AGT TGG AGG      923
Val Ser Glu Asn Pro Tyr Ser Thr Leu Trp Ser Phe Leu Ser Trp Arg

CGC AAG CTG CTT GCT CAG AAG AGC CAT GAC AAT GCT CAG CTA ATC ACG      971
Arg Lys Leu Leu Ala Gln Lys Ser His Asp Asn Ala Gln Leu Ile Thr

GGC AGG TCC TTC CAA GGC ACC ACC ATT GGC CTG GCC CCC CTC ATG GCC     1019
Gly Arg Ser Phe Gln Gly Thr Thr Ile Gly Leu Ala Pro Leu Met Ala

ATG TGC TCC GTG TAC CAG TCT GGA GGA GTT AGC ATG GAC CAC TCC GAG     1067
Met Cys Ser Val Tyr Gln Ser Gly Gly Val Ser Met Asp His Ser Glu

AAT GCC ATT GGT GTA GCC TCC ACT GTG GCC CAT GAG ATT GGC CAC AAC     1115
Asn Ala Ile Gly Val Ala Ser Thr Val Ala His Glu Ile Gly His Asn

TTT GGC ATG AGC CAT GAT TCT GCA CAC TGC TGT TCT GCC AGT GCA GCC     1163
Phe Gly Met Ser His Asp Ser Ala His Cys Cys Ser Ala Ser Ala Ala

GAT GGC GGC TGC ATC ATG GCC GCC GCC ACC GGG CAC CCT TTC CCC AAA     1211
Asp Gly Gly Cys Ile Met Ala Ala Ala Thr Gly His Pro Phe Pro Lys
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GTG TTC AGT TGG TGT AAC AGG AAG GAG CTG GAC AGG TAT CTG CAG ACA      1259
Val Phe Ser Trp Cys Asn Arg Lys Glu Leu Asp Arg Tyr Leu Gln Thr

GGA GGA GGG ATG TGT CTC TCC AAC ATG CCG GAC ACT AGG ACG CTG TAT      1307
Gly Gly Gly Met Cys Leu Ser Asn Met Pro Asp Thr Arg Thr Leu Tyr

GGA GGC CGG AGG TGT GGC AAC GGG TAC CTG GAA GAC GGT GAA GAA TGT      1355
Gly Gly Arg Arg Cys Gly Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys

GAC TGT GGA GAA GAG GAG GAA TGT AAG AAC CCT TGC TGC AAT GCC TCC      1403
Asp Cys Gly Glu Glu Glu Glu Cys Lys Asn Pro Cys Cys Asn Ala Ser

AAC TGC ACT CTG AAG GAA GGG GCA GAG TGT GCC CAT GGT TCC TGC TGC      1451
Asn Cys Thr Leu Lys Glu Gly Ala Glu Cys Ala His Gly Ser Cys Cys

CAC CAG TGC AAG CTG GTG GCT CCT GGA ACC CAG TGT CGG GAG CAG GTT      1499
His Gln Cys Lys Leu Val Ala Pro Gly Thr Gln Cys Arg Glu Gln Val

CGG CAA TGT GAC CTC CCC GAG TTC TGC ACC GGC AAG TCT CCC CAC TGC      1547
Arg Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys Ser Pro His Cys

CCC ACC AAC TAT TAT CAG ATG GAT GGC ACC CCC TGC GAG GGT GGC CAG      1595
Pro Thr Asn Tyr Tyr Gln Met Asp Gly Thr Pro Cys Glu Gly Gly Gln

GCC TAC TGC TAC AAC GGC ATG TGC CTC ACT TAC CAG GAA CAG TGC CAG      1643
Ala Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln

CAG CTG TGG GGA CCT GGA GCC CGG CCT GCC CTC GAT CTT TGC TTT GAG      1691
Gln Leu Trp Gly Pro Gly Ala Arg Pro Ala Leu Asp Leu Cys Phe Glu

AGG GTG AAT GCT GCT GGT GAC ACC TAT GGA AAC TGT GGC AAG GGC TTG      1739
Arg Val Asn Ala Ala Gly Asp Thr Tyr Gly Asn Cys Gly Lys Gly Leu

AAT GGC CAA TAC AGG AAG TGC AGT CCC AGG GAT GCC AAG TGT GGS AAG      1787
Asn Gly Gln Tyr Arg Lys Cys Ser Pro Arg Asp Ala Lys Cys Xaa Lys

ATT CAG TGC CAG AGC ACC CAG GCC CGG CCC CTG GAA TCC AAC GCA GTA      1835
Ile Gln Cys Gln Ser Thr Gln Ala Arg Pro Leu Glu Ser Asn Ala Val

TCT ATT GAC ACC ACC ATC ACC TTG AAC GGG AGG CGG ATC CAC TGT CGG      1883
Ser Ile Asp Thr Thr Ile Thr Leu Asn Gly Arg Arg Ile His Cys Arg

GGC ACC CAC GTC TAC CGG GGT CCT GAG GAG GAG GAA GGG GAA GGT GAC      1931
Gly Thr His Val Tyr Arg Gly Pro Glu Glu Glu Glu Gly Glu Gly Asp

ATG CTG GAC CCA GGG CTG GTG ATG ACT GGA ACC AAG TGT GGC CAC AAC      1979
Met Leu Asp Pro Gly Leu Val Met Thr Gly Thr Lys Cys Gly His Asn

CAT ATT TGC TTC GAG GGG CAG TGC AGG AAC ACC TCC TTC TTT GAG ACG      2027
His Ile Cys Phe Glu Gly Gln Cys Arg Asn Thr Ser Phe Phe Glu Thr

GAA GGC TGT GGG AAA AAG TGC AAT GGC CAC GGG GTC TGC AAC AAC AAC      2075
Glu Gly Cys Gly Lys Lys Cys Asn Gly His Gly Val Cys Asn Asn Asn

AAG AAC TGT CAT TGC TTC CCT GGC TGG TCT CCA CCT TTC TGT AAC ACC      2123
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Lys Asn Cys His Cys Phe Pro Gly Trp Ser Pro Pro Phe Cys Asn Thr

CCG GGA GAT GGT GGC AGC GTC GAC AGT GGT CCT TTG CCC CCT AAG AGT     2171
Pro Gly Asp Gly Gly Ser Val Asp Ser Gly Pro Leu Pro Pro Lys Ser

GTG GGT CCC GTG ATC GCT GGG GTG TTT TCA GCT CTC TTC GTG TTG GCA     2219
Val Gly Pro Val Ile Ala Gly Val Phe Ser Ala Leu Phe Val Leu Ala

GTT CTG GTG CTA CTG TGT CAC TGC TAC AGA CAG AGC CAC AAA CTG GGC     2267
Val Leu Val Leu Leu Cys His Cys Tyr Arg Gln Ser His Lys Leu Gly

AAA CCC TCG GCT CTC CCT TTC AAG CTG CGG CAT CAG TTC AGT TGT CCC     2315
Lys Pro Ser Ala Leu Pro Phe Lys Leu Arg His Gln Phe Ser Cys Pro

TTC AGG GTA TCT CAG AGT GGT GGA ACT GGC CAT GCC AAC CCA ACT TTC     2363
Phe Arg Val Ser Gln Ser Gly Gly Thr Gly His Ala Asn Pro Thr Phe

AAG TTG CAG ACC CCC CAG GGC AAG CGA AAG GTG ACT AAC ACC CCT GAA     2411
Lys Leu Gln Thr Pro Gln Gly Lys Arg Lys Val Thr Asn Thr Pro Glu

TCC CTC CGG AAG CCG TCC CAC CCC CCT CTC CGG CCC CCT CCA GAC TAC     2459
Ser Leu Arg Lys Pro Ser His Pro Pro Leu Arg Pro Pro Pro Asp Tyr

CTG CGC GTT GAA TCG CCA CCT GCA CCA TTG TCG GCA CAT CTG AAC AGG     2507
Leu Arg Val Glu Ser Pro Pro Ala Pro Leu Ser Ala His Leu Asn Arg

GCT GCT GGG AGC TCC CCA GAA GCT GGG GCT CGA ATA GAA AGA AAG GAG     2555
Ala Ala Gly Ser Ser Pro Glu Ala Gly Ala Arg Ile Glu Arg Lys Glu

TCA GCC AGG AGG CCT CCC CCA AGC CGA CCC ATG CCC CCT GCA CCT AAC     2603
Ser Ala Arg Arg Pro Pro Pro Ser Arg Pro Met Pro Pro Ala Pro Asn

TGC CTA CTG TCC CAG GAC TTC TCC AGG CCT CGA CCA CCT CAG AAG GCA     2651
Cys Leu Leu Ser Gln Asp Phe Ser Arg Pro Arg Pro Pro Gln Lys Ala

CTC CCA GCC AAT CCG GTG CCA GGC CAA AGG ACC GGT CCC AGG TCA GGA     2699
Leu Pro Ala Asn Pro Val Pro Gly Gln Arg Thr Gly Pro Arg Ser Gly

GGC ACC TCC CTG CTT CAG CCC CCT ACT TCT GGT CCT CAG CCC CCC AGG     2747
Gly Thr Ser Leu Leu Gln Pro Pro Thr Ser Gly Pro Gln Pro Pro Arg

CCT CCA GCA GTG CCT GTT CCA AAG CTA CCC GAG TAC CGA TCA CAG AGG     2795
Pro Pro Ala Val Pro Val Pro Lys Leu Pro Glu Tyr Arg Ser Gln Arg

GTT GGA GCA ATA ATT AGC TCC AAG ATC TAGAAGTGTC GAGAAGTTTC           2842
Val Gly Ala Ile Ile Ser Ser Lys Ile

TTGTTCCGAT GGAAGACTCC GGATGCCATG GAAGGTCCAG AAGAAAGACG CCTTCTCACC   2902
CATCCTGAAG CTTTGGCAGC CTTCTGGAAC GTCCCTCATC CCCAGAATCT CCCTTCTTAC   2962
CCGAGTGCCT CCTGCTTCCT CCGAGGCCCA GGGGGACTCA TATCCAATGG CTCCTAAGTG   3022
TTTGTCCTGT GCAATATACA GCCCAGGGAG GGAAGGGAAG CACGGCGAGG AGGGTGGGAA   3082
AGGTTCTCCC TCAGCCCACT AGCCAAGAGC TACCAGCGAT GCTCAGGGAA GGCTTGAGCT   3142
GGGGTCCTCC TCTGCGGAGC TTGGAGAAGG TACCCATCCT GGTCCTATGC TGGCAGGAAC   3202
ACACGCGAGT GTCACTGATT GGCCTCCTTC TGGGATCCCA GGCTGCTGAG GAAGCTACTG   3262
CTACATCCCT ACCCCAAGGG GCTTGGTCAA GGTGCCTGTC CTGGCTCTCT GGCTGCATGT   3322
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AATAAGCCAT GCTCCCCTCC CCTGCCTTTC TTCACATTCC CACTCCCATA TTTACACGGG   3382
TCACTCTGAC TCAGACAGGT ACTATTTGTA AGTAGCATAG ACAGCAGGGG GGTGGGGTGG   3442
TCAACCTGTG TCCCCTCTGA GCCGTTATGC CAAAGGTCAC TAAGGACATT TAGAATCCCC   3502
ATCCATCCAT CCATCCATCC ATCCATCCAT CCATTCATCC ATCCCCAGTG TTCCATGTGT   3562
CACCTTCTCC TTTTCCAGCA TCCCTATCCT ATGGTGCTTT GGTGGTGAAC TATGGCAGTC   3622
CTGACTTGCT GATGACCATA TGCTGGTGAC CTACAAATCG GGATCCTGCC ATATGGGGTC   3682
GCCACTGGAC TTTCTGCACT GGTTCTCAAG AGCGTTGAGC CGAGTGGGCG TGTATGTTTG   3742
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AAAGAGACAG AGGCAATGAG AGAGACAGAC ATGCAGGCAG GCCGACAGCT CTGCATGTAC   3862
TTGTGTTTTA CGGCCTCAAG CAGTATAAGG GACCTCCTCC TTATTTCTGA CTCATATCTA   3922
AGTAAGGTTC CCCAGGACAG CCACAGCTGT ACTGAGGGGG GCTGACATGT TTGGCATCCT   3982
GGCTATAGTA TTGTATACAC AGGGCCACCA GCCCCGCCCT AGTGGTCAGC TCTGAGGGGG   4042
GACTGGTGAC TCTGAACAGA TCGATGTCAA CAGCCATGGT GAACCAGATC TGGGCAGGGT   4102
TCCCCAAACT CTATTCAACC AGAGTTTTAT CACGCACTCA TCGGGTCTCT CCTGGTTGCT   4162
GCCCCGAGGT GATCGTCATG GAAAATGCTG AGAAGGTGGG AATGGGATGG GGTGGACCTT   4222
CTCTTGCTTG GTGCTCCGCT ATTTGGAACA GTTCTTACAC ATTTGCTGGG CCTGGCCTCT   4282
GAGAGGCCAT CTTCCACCCC CAGAAAGGTG CTAATGGCAC TGCAGAGGGC TCTCTAGGGG   4342
CCTCCCCGCC CCAACAGCAA GCAGTTGTTA GCTCTTGGAA CCCTCCAGAG GAAGAGGCAA   4402
GCGTTTGACT TCCCCTTTAC CACCTGAGGC CTCCTTATAT CTCTTCCCAG AGTAAGCTTT   4462
GGGATTGTAG ACATGTGGGA GCTATGACAG ACGTGGCCTG GGGTAGAAAG ATCTCAGGAA   4522
AGCACCTTTC TCCTTTTCAG GGTGACCGTG CTCTTCACAC TCTCTGAGGC CTCAGTCCAT   4582
GTCCTATATC AGTTTCTCTT TTGTGTGCTT TACCAAGTGG CCGGTGACTA CAGGCCACCC   4642
CGATTCTCAC CACAAAGTTA GAAACCCTCC ACTTTCTGTC CCTTGAACCA TATCAGAAAA   4702
AGACCCATTT CCTTGCTCTT TGGTAATCAC TTCTGTTTTT TCTTCTTCAT TACTGTGCTA   4762
CCACCTCCAT CCCATGACAT TATTCTGTGA GTGTAAGAGG ACGGTGTTTT TTATCTTGGG   4822
AGAATGTCGG CAGCTGCTCT ACACACAACT TCACTCAAGG CTTTGTCTCC AGAGGCCAGC   4882
TAGGCTGTCA CAGGCAGGAA TCCCTTCCCA TCTGCTTTGT GAAGGGTCCC ATACAGGTGT   4942
ATCTAGACTT CAAGGACAGG GTTTGTCTCA CAGGATTGTC ACTTAGGAGA TGAAAGAATA   5002
TTACCACATG AGGAGGAGGG GCAGTTGCAA CAGAACACTT TGGTCTTCCT ACACCAAGTC   5062
TGTGAGGGCA TCCAAGACTG AATGAAAGCG CTTTTCTTAT GCATACAATG TGAGCAAGAA   5122
CAAGAACTGT TTAAGGCACC TCTGTTCCCA GCCACTGAAG AGAGACGTCA GAAGATGTTA   5182
GAATAGGTCA AAACCAAGGC TCTGGTGGAC TGAGGGAAGG TTTGTAGCTG CGTTTAGTGG   5242
TATACATCTT TAGTCCCAGC ATAGGCAGGT GAATCTCGAG TTTGAAGCTA GCCTGGTCTA   5302
AAAAGGAAGT TCCAAGACTG CCAGGGCCAC ACAGAGGAAA AAAAAAAACC CTCTAGAAAA   5362
ACAAAAATGA AGACAGGTTC TCATGTATCG TAGATTGGCC TTTAAGTCAC TTTACCAAGG   5422
ATGATCTTTG AACTCCTGAG TACAGACTGC GGGTGTGTGC TACCATGCTT TATGTGGCCC   5482
TGGGTTCAAA CACAGCCCTT CATATGTATA TAGCCAAACA CTCTACAACT GAGCTACATC   5542
CTCCAGCCTA GGCTGTAAAT GTTTTTTGGA GCTAGATTAG CTGCCTGCCA ACCTTAGAAC   5602
TGCAAAGCCA TTCCTGACCT GTAAACCTCA GCTCTCCATC TCTATAAGAG GTATAGCCTG   5662
GGCTAATACC GTCCAAGTTA CAACTCCTTG CTTGCTTTCT GTTCCTTCTA GCCTTGGTGA   5722
CTTCCACCAG GAAGAGAATA CCCCCTCTCT ACCCCTGCTC CAAGACACTG TAGATGCTAG   5782
TGTCGGAGTG TTCTCTGTAA CGCGACAGTT CCTTCTGTTG CAATAGCCCC CCTGCAACAC   5842
TGCAATAATC CTTCAGTGTC TCCCCTGGGC TCAATTCACT TCCTTATTTG ACAAAGTGGA   5902
GGTGAGACTT GTATTCTTAA AATTGGAGGC TAGTTATTTT GTCAAATGCA TGTAATGAAC   5962
AGACCCGAAG GAATCCTCCA CACACAAGCC AGGGAACACC AACTGGAAAG GTACCCCGTC   6022
CCAGGGAAGC CTGCTAGGGA GAGGTTCTGT AGAATCCGAG CCTAGCACCC CAAAGTCATG   6082
CACCCAGTAT CCTCTTGTAT GACTGTATAT GTCTATGTCT GGGATCCAGG GCAAATGTGA   6142
ATTTCCTTTT GATTTGGGAG ATTGTTCACA GGAAGTAGTC CTCCCCTCTC ATGTCCTCCT   6202
ATTGATTGTT TACAATATTT GTACATCTAT GCAAAATACT TGAATGGGCC ATGGTGCCTT   6262
GTTTTTTGTT GTTGTTGTTA TTTTTTTCTC CTTGTTTGTA TTTAATTAAA ACAAATTGTC   6322
ATGAGGAAAA AAAAAAAAAA AAA                                           6345
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SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 920 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Pro Gly Arg Ala Gly Val Ala Arg Phe Cys Leu Leu Ala Leu Ala
Leu Gln Leu His Trp Pro Leu Ala Ala Cys Glu Pro Gly Trp Thr Thr
Arg Gly Ser Gln Glu Gly Ser Pro Pro Leu Gln His Glu Leu Ile Ile
Pro Gln Trp Arg Thr Ser Glu Ser Pro Gly Arg Gly Lys His Pro Leu
Arg Ala Glu Leu Arg Val Met Ala Glu Gly Arg Glu Leu Ile Leu Asp
Leu Glu Lys Asn Glu His Leu Phe Ala Pro Ala Tyr Thr Glu Thr Cys
Tyr Thr Ala Ser Gly Asn Pro Gln Thr Ser Thr Leu Lys Ser Glu Asp
His Cys Phe Tyr His Gly Thr Val Arg Asp Val Asp Glu Ser Ser Val
Thr Leu Ser Thr Cys Arg Gly Ile Arg Gly Leu Ile Ile Val Arg Ser
Asn Leu Ser Tyr Ile Ile Glu Pro Val Pro Asn Ser Asp Ser Gln His
Arg Ile Tyr Arg Ser Glu His Leu Thr Leu Pro Pro Gly Asn Cys Gly
Phe Glu His Ser Gly Pro Thr Ser Lys Asp Trp Ala Leu Gln Phe Thr
His Gln Thr Lys Lys Gln Pro Arg Arg Met Lys Arg Glu Asp Leu His
                                          -1  1
Ser Met Lys Tyr Val Glu Leu Tyr Leu Val Ala Asp Tyr Ala Glu Phe
Gln Lys Asn Arg His Asp Gln Asp Ala Thr Lys Arg Lys Leu Met Glu
Ile Ala Asn Tyr Val Asp Lys Phe Tyr Arg Ser Leu Asn Ile Arg Ile
Ala Leu Val Gly Leu Glu Val Trp Thr His Gly Asp Lys Cys Glu Val
Ser Glu Asn Pro Tyr Ser Thr Leu Trp Ser Phe Leu Ser Trp Arg Arg
Lys Leu Leu Ala Gln Lys Ser His Asp Asn Ala Gln Leu Ile Thr Gly
Arg Ser Phe Gln Gly Thr Thr Ile Gly Leu Ala Pro Leu Met Ala Met
Cys Ser Val Tyr Gln Ser Gly Gly Val Ser Met Asp His Ser Glu Asn
Ala Ile Gly Val Ala Ser Thr Val Ala His Glu Ile Gly His Asn Phe
Gly Met Ser His Asp Ser Ala His Cys Cys Ser Ala Ser Ala Ala Asp
Gly Gly Cys Ile Met Ala Ala Ala Thr Gly His Pro Phe Pro Lys Val
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Phe Ser Trp Cys Asn Arg Lys Glu Leu Asp Arg Tyr Leu Gln Thr Gly

Gly Gly Met Cys Leu Ser Asn Met Pro Asp Thr Arg Thr Leu Tyr Gly

Gly Arg Arg Cys Gly Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp

Cys Gly Glu Glu Glu Glu Cys Lys Asn Pro Cys Cys Asn Ala Ser Asn

Cys Thr Leu Lys Glu Gly Ala Glu Cys Ala His Gly Ser Cys Cys His

Gln Cys Lys Leu Val Ala Pro Gly Thr Gln Cys Arg Glu Gln Val Arg

Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro

Thr Asn Tyr Tyr Gln Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala

Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln Gln

Leu Trp Gly Pro Gly Ala Arg Pro Ala Leu Asp Leu Cys Phe Glu Arg

Val Asn Ala Ala Gly Asp Thr Tyr Gly Asn Cys Gly Lys Gly Leu Asn

Gly Gln Tyr Arg Lys Cys Ser Pro Arg Asp Ala Lys Cys Xaa Lys Ile

Gln Cys Gln Ser Thr Gln Ala Arg Pro Leu Glu Ser Asn Ala Val Ser

Ile Asp Thr Thr Ile Thr Leu Asn Gly Arg Arg Ile His Cys Arg Gly

Thr His Val Tyr Arg Gly Pro Glu Glu Glu Glu Gly Glu Gly Asp Met

Leu Asp Pro Gly Leu Val Met Thr Gly Thr Lys Cys Gly His Asn His

Ile Cys Phe Glu Gly Gln Cys Arg Asn Thr Ser Phe Phe Glu Thr Glu

Gly Cys Gly Lys Lys Cys Asn Gly His Gly Val Cys Asn Asn Asn Lys

Asn Cys His Cys Phe Pro Gly Trp Ser Pro Pro Phe Cys Asn Thr Pro

Gly Asp Gly Gly Ser Val Asp Ser Gly Pro Leu Pro Pro Lys Ser Val

Gly Pro Val Ile Ala Gly Val Phe Ser Ala Leu Phe Val Leu Ala Val

Leu Val Leu Leu Cys His Cys Tyr Arg Gln Ser His Lys Leu Gly Lys

Pro Ser Ala Leu Pro Phe Lys Leu Arg His Gln Phe Ser Cys Pro Phe

Arg Val Ser Gln Ser Gly Gly Thr Gly His Ala Asn Pro Thr Phe Lys

Leu Gln Thr Pro Gln Gly Lys Arg Lys Val Thr Asn Thr Pro Glu Ser

Leu Arg Lys Pro Ser His Pro Pro Leu Arg Pro Pro Pro Asp Tyr Leu

Arg Val Glu Ser Pro Pro Ala Pro Leu Ser Ala His Leu Asn Arg Ala

Ala Gly Ser Ser Pro Glu Ala Gly Ala Arg Ile Glu Arg Lys Glu Ser

Ala Arg Arg Pro Pro Pro Ser Arg Pro Met Pro Pro Ala Pro Asn Cys

Leu Leu Ser Gln Asp Phe Ser Arg Pro Arg Pro Pro Gln Lys Ala Leu

Pro Ala Asn Pro Val Pro Gly Gln Arg Thr Gly Pro Arg Ser Gly Gly

Thr Ser Leu Leu Gln Pro Pro Thr Ser Gly Pro Gln Pro Pro Arg Pro

Pro Ala Val Pro Val Pro Lys Leu Pro Glu Tyr Arg Ser Gln Arg Val

Gly Ala Ile Ile Ser Ser Lys Ile
716

SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3928 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B)CLONE: JM109(pBSMel γ)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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GTTGCAAGGA TGACCGAAGC GGAGGCGGCG GCCGCGCGTT GAGCGGAACC TGCCGAAGCC      60

CTCGCT ATG GGG CCG CGC GCG CTC TCG CCC CTT GCC TCT CTG CGA CTA          108
       Met Gly Pro Arg Ala Leu Ser Pro Leu Ala Ser Leu Arg Leu

AGG TGG CTG CTG GCG TGT GGC TTG CTG GGC CCA GTC CTC GAG GCC GGG        156
Arg Trp Leu Leu Ala Cys Gly Leu Leu Gly Pro Val Leu Glu Ala Gly

CGA CCA GAC TTG GAA CAG ACT GTC CAT CTT TCT TCT TAT GAA ATT ATT        204
Arg Pro Asp Leu Glu Gln Thr Val His Leu Ser Ser Tyr Glu Ile Ile

ACT CCT TGG AGA TTA ACT AGA GAA AGA AGG GAA GCT CTG GGG CCC AGT        252
Thr Pro Trp Arg Leu Thr Arg Glu Arg Arg Glu Ala Leu Gly Pro Ser

TCA CAG CAG ATC TCT TAC GTC ATC CAG GCC CAA GGA AAA CAG CAT ATT        300
Ser Gln Gln Ile Ser Tyr Val Ile Gln Ala Gln Gly Lys Gln His Ile

ATT CAC TTG GAA AGA AAC ACA GAC CTT TTA CCT AAT GAT TTT GTA GTT        348
Ile His Leu Glu Arg Asn Thr Asp Leu Leu Pro Asn Asp Phe Val Val

TAC ACC TAC GAC AAG GAA GGC TCC CTA CTC TCT GAC CAT CCC AAC GTA        396
Tyr Thr Tyr Asp Lys Glu Gly Ser Leu Leu Ser Asp His Pro Asn Val

CAG AGC CAT TGT CAC TAT CGA GGC TAT GTG GAG GGA GTG CAG AAT TCC        444
Gln Ser His Cys His Tyr Arg Gly Tyr Val Glu Gly Val Gln Asn Ser

GCG GTT GCT GTG AGC GCC TGC TTT GGA CTC AGA GGC TTG CTG CAT TTG        492
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Ala Val Ala Val Ser Ala Cys Phe Gly Leu Arg Gly Leu Leu His Leu

GAG AAT GCC AGT TTT GGA ATT GAA CCT CTG CAC AAC AGC TCA CAC TTT      540
Glu Asn Ala Ser Phe Gly Ile Glu Pro Leu His Asn Ser Ser His Phe

GAG CAC ATA TTT TAC CCC ATG GAT GGC ATC CAC CAG GAG CCT CTG AGA      588
Glu His Ile Phe Tyr Pro Met Asp Gly Ile His Gln Glu Pro Leu Arg

TGT GGA GTC TCT AAC AGG GAC ACA GAG AAG GAA GGC ACA CAG GGG GAT      636
Cys Gly Val Ser Asn Arg Asp Thr Glu Lys Glu Gly Thr Gln Gly Asp

GAG GAG GAG CAT CCG AGT GTC ACT CAG CTG CTG CGC AGA AGA AGA GCT      684
Glu Glu Glu His Pro Ser Val Thr Gln Leu Leu Arg Arg Arg Arg Ala

GTT CTA CCA CAG ACC CGC TAT GTG GAG CTG TTC ATT GTT GTA GAC AAG      732
Val Leu Pro Gln Thr Arg Tyr Val Glu Leu Phe Ile Val Val Asp Lys

GAA AGG TAC GAC ATG ATG GGA CGG AAC CAG ACT GCT GTG AGA GAA GAG      780
Glu Arg Tyr Asp Met Met Gly Arg Asn Gln Thr Ala Val Arg Glu Glu

ATG ATT CGC TTA GCA AAC TAC CTG GAT AGC ATG TAC ATC ATG TTA AAC      828
Met Ile Arg Leu Ala Asn Tyr Leu Asp Ser Met Tyr Ile Met Leu Asn

ATT CGA ATT GTG CTG GTT GGA CTA GAA ATT TGG ACA GAC AGA AAT CCT      876
Ile Arg Ile Val Leu Val Gly Leu Glu Ile Trp Thr Asp Arg Asn Pro

ATC AAT ATA ATT GGA GGA GCT GGA GAT GTG CTG GGC AAC TTT GTT CAG      924
Ile Asn Ile Ile Gly Gly Ala Gly Asp Val Leu Gly Asn Phe Val Gln

TGG CGG GAA AAG TTC CTT ATA ACT CGT CGG AGA CAC GAC AGT GCA CAG      972
Trp Arg Glu Lys Phe Leu Ile Thr Arg Arg Arg His Asp Ser Ala Gln

TTG GTT TTG AAG AAA GGC TTT GGT GGA ACT GCA GGA ATG GCG TTT GTA     1020
Leu Val Leu Lys Lys Gly Phe Gly Gly Thr Ala Gly Met Ala Phe Val

GGA ACA GTA TGT TCA AGG AGC CAC GCA GGT GGG ATC AAT GTG TTT GGG     1068
Gly Thr Val Cys Ser Arg Ser His Ala Gly Gly Ile Asn Val Phe Gly

CAA ATC ACT GTG GAG ACA TTT GCA TCC ATT GTT GCT CAT GAA TTG GGG     1116
Gln Ile Thr Val Glu Thr Phe Ala Ser Ile Val Ala His Glu Leu Gly

CAT AAC CTT GGA ATG AAT CAT GAT GAT GGG AGA GAG TGT TTC TGT GGA     1164
His Asn Leu Gly Met Asn His Asp Asp Gly Arg Glu Cys Phe Cys Gly

GCA AAG AGC TGT ATC ATG AAT TCA GGA GCA TCC GGG TCC AGA AAC TTT     1212
Ala Lys Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe

AGC AGT TGC AGT GCG GAG GAC TTT GAG AAG TTA ACG TTG AAT AAG GGA     1260
Ser Ser Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly

GGA AGC TGC CTG CTT AAC ATC CCG AAG CCT GAC GAA GCC TAC AGC GCG     1308
Gly Ser Cys Leu Leu Asn Ile Pro Lys Pro Asp Glu Ala Tyr Ser Ala

CCC TCC TGT GGT AAT AAG CTG GTG GAC CCT GGA GAG GAG TGT GAC TGC     1356
Pro Ser Cys Gly Asn Lys Leu Val Asp Pro Gly Glu Glu Cys Asp Cys
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GGC ACA GCG AAG GAG TGT GAG GTG GAC CCA TGC TGT GAA GGA AGC ACT     1404
Gly Thr Ala Lys Glu Cys Glu Val Asp Pro Cys Cys Glu Gly Ser Thr

TGT AAG CTC AAG TCA TTT GCT GAG TGT GCA TAT GGC GAC TGT TGT AAA     1452
Cys Lys Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly Asp Cys Cys Lys

GAT TGC CAG TTC CTT CCA GGA GGC TCC ATG TGC AGA GGG AAG ACC AGT     1500
Asp Cys Gln Phe Leu Pro Gly Gly Ser Met Cys Arg Gly Lys Thr Ser

GAG TGT GAT GTT CCT GAG TAC TGC AAC GGT TCC TCT CAG TTC TGC CCG     1548
Glu Cys Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser Gln Phe Cys Pro

CCA GAT GTC TTC ATT CAG AAT GGA TAT CCT TGC CAG AAC AGC AAA GCC     1596
Pro Asp Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln Asn Ser Lys Ala

TAC TGC TAC AAT GGC ATG TGC CAA TAT TAT GAC GCG CAG TGT CAG GTC     1644
Tyr Cys Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala Gln Cys Gln Val

ATC TTT GGT TCA AAG GCT AAG GCT GCC CCA AGA GAT TGC TTC ATT GAA     1692
Ile Phe Gly Ser Lys Ala Lys Ala Ala Pro Arg Asp Cys Phe Ile Glu

GTC AAT TCT AAA GGT GAC AGA TTT GGC AAC TGT GGT TTC TCC GGC AGT     1740
Val Asn Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Ser

GAG TAC AAG AAG TGT GCC ACT GGG AAC GCG CTG TGT GGA AAG CTT CAA     1788
Glu Tyr Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln

TGC GAG AAT GTA CAG GAC ATG CCG GTG TTT GGA ATA GTA CCA GCT ATC     1836
Cys Glu Asn Val Gln Asp Met Pro Val Phe Gly Ile Val Pro Ala Ile

ATT CAG ACA CCC AGT CGA GGC ACC AAA TGC TGG GGT GTG GAT TTC CAG     1884
Ile Gln Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln

CTT GGT TCC GAC GTT CCA GAC CCA GGG ATG GTG AAT GAA GGC ACC AAA     1932
Leu Gly Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys

TGT GAT GCT GGC AAG ATT TGC AGG AAT TTT CAG TGT GTA AAT GCT TCT     1980
Cys Asp Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asn Ala Ser

GTC CTG AAT TAT GAC TGT GAC ATT CAG GGA AAA TGT CAT GGC CAT GGG     2028
Val Leu Asn Tyr Asp Cys Asp Ile Gln Gly Lys Cys His Gly His Gly

GTA TGT AAC AGC AAT AAG AAT TGT CAC TGT GAA GAT GGC TGG GCT CCC     2076
Val Cys Asn Ser Asn Lys Asn Cys His Cys Glu Asp Gly Trp Ala Pro

CCA CAC TGT GAC ACC AAA GGA TAT GGA GGA AGC GTG GAC AGC GGG CCG     2124
Pro His Cys Asp Thr Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly Pro

ACG TAT AAT GCA AAG AGC ACA GCA CTG AGG GAC GGG CTT CTG GTC TTC     2172
Thr Tyr Asn Ala Lys Ser Thr Ala Leu Arg Asp Gly Leu Leu Val Phe

TTC TTC CTA ATC GTC CCC CTT GTT GCG GCT GCC ATT TTC CTC TTT ATC     2220
Phe Phe Leu Ile Val Pro Leu Val Ala Ala Ala Ile Phe Leu Phe Ile
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AAG AGA GAT GAA CTA CGG AAA ACC TTC AGG AAG AAG AGA TCA CAA ATG     2268
Lys Arg Asp Glu Leu Arg Lys Thr Phe Arg Lys Lys Arg Ser Gln Met

TCA GAT GGC AGA AAT CAA GCA AAC GTC TCT AGA CAG CCA GGA GAT CCT     2316
Ser Asp Gly Arg Asn Gln Ala Asn Val Ser Arg Gln Pro Gly Asp Pro

AGT ATC TCC AGA CCA CCA GGG GGC CCA AAT GTC TCC AGA CCA CCA GGG     2364
Ser Ile Ser Arg Pro Pro Gly Gly Pro Asn Val Ser Arg Pro Pro Gly

GGC CCA GGT GTC TCC AGA CCA CCA GGG GGC CCA GGT GTC TCC AGA CCA     2412
Gly Pro Gly Val Ser Arg Pro Pro Gly Gly Pro Gly Val Ser Arg Pro

CCA GGG GGC CCA GGT GTC TCC AGA CCG CCA CCT GGG CAT GGA AAC AGA     2460
Pro Gly Gly Pro Gly Val Ser Arg Pro Pro Pro Gly His Gly Asn Arg

TTC CCA GTA CCA ACC TAC GCC GCC AAG CAG CCT GCG CAG TTC CCG TCA     2508
Phe Pro Val Pro Thr Tyr Ala Ala Lys Gln Pro Ala Gln Phe Pro Ser

AGG CCA CCT CCA CCA CAA CCG AAA ATA TCT TCT CAG GGA AAC TTG ATT     2556
Arg Pro Pro Pro Pro Gln Pro Lys Ile Ser Ser Gln Gly Asn Leu Ile

CCG GCT CGG CCC GCT CCT GCA CCT CCT TTA TAT AGC TCC CTC ACC         2601
Pro Ala Arg Pro Ala Pro Ala Pro Pro Leu Tyr Ser Ser Leu Thr

TGATAGTAGA ATATTAGAAT CTTATTTTTT AAATGTCTTC AGGGAACTGA GCAAATGTTT  2661
GTTGTTTTTT TTTTCCTGAT GTTTTCTTGA AAAGCCTTTC TCTTCCAACC ATGAATGAAC  2721
ACAAACCACC ACAAAACAAG CTTTATTAAC ACAGGAGCCT AGTGGGGATT GCGAAACACA  2781
GGAATGTGCA GGCGCTCCGG GGGGTGTAAA GTGAACGTTT CCATCGTTAG AATGTTTTCT  2841
CTGGCCATTT GTGGATTTAA TGCACTTGAC GTGGATTAAG TTATTCTGAG CATGTTACTG  2901
TAATGATTCT CAAATTAACT GTATTAGTGT AAGCTTTGTC ACTATGCGCT AAACGTAATC  2961
CTGACTTTTT GACCCCAGTT ACCATTAATA GTTTCTGGTT GACCATTTGA ACATGTATTA  3021
ACTTAGGAAG ACTAATTGCC AATAACGTCT GCATTTTCAT CTTGCATGGA TTAACAGCCA  3081
TTTATATGGA CTTATGTCTC TTAATGCACA AAGAAGCAGA TATCTCGAAG GAGCTTACAC  3141
AAGAACCACA ATTACTAGAT CATGATATAC TTGGAAAGTG TGAAATATGG TGTGTACTCA  3201
GTTATTGGCT TCCATTTTTA TGATCTTTCA ACTATAACAA TTATGATAGA AATCGATTTA  3261
ACACAATCAG TTATGGGCTT CCATTTTCAA ATATCTTTTC AACTGTAATG ACTATGACAG  3321
GAACTGATTC AACTCTCAAT TTTCTTTATG CATCATGGTA AAGCATTGCA GCAGTGTTGT  3381
TTTGTTTGAA GTGCACACTC TATGGTACGA GGTGTTTAGT ATACCCAAGC AGATAGGTGT  3441
CGATCGAACA GGAGCAGGGA GAATACTTCC AACAGTTGAG GTGTTACCAA ACCACTTGAG  3501
AATTCATGAG CACTTTAACT CTAAACTCTG AATTTCAAAG CTTGATGTGA AGTCCTCTAG  3561
AATGTTTACA TTTACTAAGG TGTGCTGGGT CCTGTCTCTT TTGACTAATA TTTTCGTAAA  3621
CATTAGGCTG GAGAAAGGAA GGAAGCAGTG GTTTCCTTAG ATAACTACAG AATTATACTG  3681
GTCTCTGGGA TTACTCTCTC AGCTGTATTA AAATGAATTT GTACTTTGAA AGGAATGATA  3741
TTGACACTAA AATTTTAAAC ATTTAAATTT TTTCATAATC TTTCATAAAG AAGTTTAATA  3801
ATAGGTATAT TAACTGAATT TCATTAGTTT TTTAAAATAA TATTGTTTGT GTATATATAC  3861
ATATTAAAAT AAAAACATTT ACAACAAATA AAATACTTGA AATTCTAAAA AAAAAAAAAA  3921
AAAAAAA                                                           3928
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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 845 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Pro Arg Ala Leu Ser Pro Leu Ala Ser Leu Arg Leu Arg Trp
Leu Leu Ala Cys Gly Leu Leu Gly Pro Val Leu Glu Ala Gly Arg Pro
Asp Leu Glu Gln Thr Val His Leu Ser Ser Tyr Glu Ile Ile Thr Pro
Trp Arg Leu Thr Arg Glu Arg Arg Glu Ala Leu Gly Pro Ser Ser Gln
Gln Ile Ser Tyr Val Ile Gln Ala Gln Gly Lys Gln His Ile Ile His
Leu Glu Arg Asn Thr Asp Leu Leu Pro Asn Asp Phe Val Val Tyr Thr
Tyr Asp Lys Glu Gly Ser Leu Leu Ser Asp His Pro Asn Val Gln Ser
His Cys His Tyr Arg Gly Tyr Val Glu Gly Val Gln Asn Ser Ala Val
Ala Val Ser Ala Cys Phe Gly Leu Arg Gly Leu Leu His Leu Glu Asn
Ala Ser Phe Gly Ile Glu Pro Leu His Asn Ser Ser His Phe Glu His
Ile Phe Tyr Pro Met Asp Gly Ile His Gln Glu Pro Leu Arg Cys Gly
Val Ser Asn Arg Asp Thr Glu Lys Glu Gly Thr Gln Gly Asp Glu Glu
Glu His Pro Ser Val Thr Gln Leu Leu Arg Arg Arg Arg Ala Val Leu
-205 1
Pro Gln Thr Arg Tyr Val Glu Leu Phe Ile Val Val Asp Lys Glu Arg
Tyr Asp Met Met Gly Arg Asn Gln Thr Ala Val Arg Glu Glu Met Ile
Arg Leu Ala Asn Tyr Leu Asp Ser Met Tyr Ile Met Leu Asn Ile Arg
Ile Val Leu Val Gly Leu Glu Ile Trp Thr Asp Arg Asn Pro Ile Asn
Ile Ile Gly Gly Ala Gly Asp Val Leu Gly Asn Phe Val Gln Trp Arg
Glu Lys Phe Leu Ile Thr Arg Arg Arg His Asp Ser Ala Gln Leu Val
Leu Lys Lys Gly Phe Gly Gly Thr Ala Gly Met Ala Phe Val Gly Thr
Val Cys Ser Arg Ser His Ala Gly Gly Ile Asn Val Phe Gly Gln Ile
Thr Val Glu Thr Phe Ala Ser Ile Val Ala His Glu Leu Gly His Asn
Leu Gly Met Asn His Asp Asp Gly Arg Glu Cys Phe Cys Gly Ala Lys
Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe Ser Ser
Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly Gly Ser
Cys Leu Leu Asn Ile Pro Lys Pro Asp Glu Ala Tyr Ser Ala Pro Ser

Cys Gly Asn Lys Leu Val Asp Pro Gly Glu Glu Cys Asp Cys Gly Thr

Ala Lys Glu Cys Glu Val Asp Pro Cys Cys Glu Gly Ser Thr Cys Lys

Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly Asp Cys Cys Lys Asp Cys

Gln Phe Leu Pro Gly Gly Ser Met Cys Arg Gly Lys Thr Ser Glu Cys

Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser Gln Phe Cys Pro Pro Asp

Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln Asn Ser Lys Ala Tyr Cys

Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala Gln Cys Gln Val Ile Phe

Gly Ser Lys Ala Lys Ala Ala Pro Arg Asp Cys Phe Ile Glu Val Asn

Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Ser Glu Tyr

Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln Cys Glu

Asn Val Gln Asp Met Pro Val Phe Gly Ile Val Pro Ala Ile Ile Gln

Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln Leu Gly

Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys Cys Asp

Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asn Ala Ser Val Leu

Asn Tyr Asp Cys Asp Ile Gln Gly Lys Cys His Gly His Gly Val Cys

Asn Ser Asn Lys Asn Cys His Cys Glu Asp Gly Trp Ala Pro Pro His

Cys Asp Thr Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly Pro Thr Tyr

Asn Ala Lys Ser Thr Ala Leu Arg Asp Gly Leu Leu Val Phe Phe Phe

Leu Ile Val Pro Leu Val Ala Ala Ala Ile Phe Leu Phe Ile Lys Arg

Asp Glu Leu Arg Lys Thr Phe Arg Lys Lys Arg Ser Gln Met Ser Asp

Gly Arg Asn Gln Ala Asn Val Ser Arg Gln Pro Gly Asp Pro Ser Ile

Ser Arg Pro Pro Gly Gly Pro Asn Val Ser Arg Pro Pro Gly Gly Pro

Gly Val Ser Arg Pro Pro Gly Gly Pro Gly Val Ser Arg Pro Pro Gly

Gly Pro Gly Val Ser Arg Pro Pro Pro Gly His Gly Asn Arg Phe Pro

Val Pro Thr Tyr Ala Ala Lys Gln Pro Ala Gln Phe Pro Ser Arg Pro

Pro Pro Pro Gln Pro Lys Ile Ser Ser Gln Gly Asn Leu Ile Pro Ala

Arg Pro Ala Pro Ala Pro Pro Leu Tyr Ser Ser Leu Thr

640

SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 321 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B)CLONE: JM109 (pBShuMα300)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

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AAG CCT GCA GGA ACA GCG TGC AGG GAC TCC AGC AAC TCC TGT GAC CTC      48
Lys Pro Ala Gly Thr Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu

CCA GAG TTC TGC ACA GGG GCC AGC CCT CAC TGC CCA GCC AAC GTG TAC      96
Pro Glu Phe Cys Thr Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr

CTG CAC GAT GGG CAC TCA TGT CAG GAT GTG GAC GGC TAC TGC TAN AAT     144
Leu His Asp Gly His Ser Cys Gln Asp Val Asp Gly Tyr Cys Xaa Asn

GGC ATC TGC CAG ACT CAC GAG CAG CAG TGT GTC ACG CTC TGG GGA CCA     192
Gly Ile Cys Gln Thr His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro

GGT GCT AAA CCT GCC CCT GGG ATC TGC TTT GAG AGA GTC AAT TCT GCA     240
Gly Ala Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala

GGT GAA CCT TAT GGC AAC TGT GGC AAA GTC TCG AAG AGT TCC TTT GCC     288
Gly Glu Pro Tyr Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala

AAA TGC GAG ATG AGA GAT GCT AAA TGC GGC AAG                      321
Lys Cys Glu Met Arg Asp Ala Lys Cys Gly Lys
```

SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Lys Pro Ala Gly Thr Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu
 1               5                  10                  15
Pro Glu Phe Cys Thr Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr
            20                  25                  30
Leu His Asp Gly His Ser Cys Gln Asp Val Asp Gly Tyr Cys Xaa Asn
        35                  40                  45
Gly Ile Cys Gln Thr His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro
    50                  55                  60
Gly Ala Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala
65                  70                  75                  80

Gly Glu Pro Tyr Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala
                85                  90                  95
Lys Cys Glu Met Arg Asp Ala Lys Cys Gly Lys
            100                 105
```

SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 967 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE: JM109 (pBShuMγ G238)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
GCA AAG AGC TGC ATC ATG AAT TCA GGA GCA TCG GGT TCC AGA AAC TTT      48
Ala Lys Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe

AGC AGT TGC AGT GCA GAG GAC TTT GAG AAG TTA ACT TTA AAT AAA GGA      96
Ser Ser Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly

GGA AAC TGC CTT CTT AAT ATT CCA AAG CCT GAT GAA GCC TAT AGT GCT     144
Gly Asn Cys Leu Leu Asn Ile Pro Lys Pro Asp Glu Ala Tyr Ser Ala

CCC TCC TGT GGT AAT AAG TTG GTG GAC GCT GGG GAA GAG TGT GAC TGT     192
Pro Ser Cys Gly Asn Lys Leu Val Asp Ala Gly Glu Glu Cys Asp Cys

GGT ACT CCA AAG GAA TGT GAA TTG GAC CCT TGC TGC GAA GGA AGT ACC     240
Gly Thr Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys Glu Gly Ser Thr

TGT AAG CTT AAA TCA TTT GCT GAG TGT GCA TAT GGT GAC TGT TGT AAA     288
Cys Lys Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly Asp Cys Cys Lys

GAC TGT CGG TTC CTT CCA GGA GGT ACT TTA TGC CGA GGA AAA ACC AGT     336
Asp Cys Arg Phe Leu Pro Gly Gly Thr Leu Cys Arg Gly Lys Thr Ser

GAG TGT GAT GTT CCA GAG TAC TGC AAT GGT TCT TCT CAG TTC TGT CAG     384
Glu Cys Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser Gln Phe Cys Gln

CCA GAT GTT TTT ATT CAG AAT GGA TAT CCT TGC CAG AAT AAC AAA GCC     432
Pro Asp Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln Asn Asn Lys Ala

TAT TGC TAC AAC GGC ATG TGC CAG TAT TAT GAT GCT CAA TGT CAA GTC     480
Tyr Cys Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala Gln Cys Gln Val

ATC TTT GGC TCA AAA GCC AAG GCT GCC CCC AAA GAT TGT TTC ATT GAA     528
Ile Phe Gly Ser Lys Ala Lys Ala Ala Pro Lys Asp Cys Phe Ile Glu

GTG AAT TCT AAA GGT GAC AGA TTT GGC AAT TGT GGT TTC TCT GGC AAT     576
Val Asn Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Asn
```

```
GAA TAC AAG AAG TGT GCC ACT GGG AAT GCT TTG TGT GGA AAG CTT CAG      624
Glu Tyr Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln

TGT GAG AAT GTA CAA GAG ATA CCT GTA TTT GGA ATT GTG CCT GCT ATT      672
Cys Glu Asn Val Gln Glu Ile Pro Val Phe Gly Ile Val Pro Ala Ile

ATT CAA ACG CCT AGT CGA GGC ACC AAA TGT TGG GGT GTG GAT TTC CAG      720
Ile Gln Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln

CTA GGA TCA GAT GTT CCA GAT CCT GGG ATG GTT AAC GAA GGC ACA AAA      768
Leu Gly Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys

TGT GGT GCT GGA AAG ATC TGT AGA AAC TTC CAG TGT GTA GAT GCT TCT      816
Cys Gly Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asp Ala Ser

GTT CTG AAT TAT GAC TGT GAT GTT CAG AAA AAG TGT CAT GGA CAT GGG      864
Val Leu Asn Tyr Asp Cys Asp Val Gln Lys Lys Cys His Gly His Gly

GTA TGT AAT AGC AAT AAG AAT TGT CAC TGT GAA AAT GGC TGG CTC CCC      912
Val Cys Asn Ser Asn Lys Asn Cys His Cys Glu Asn Gly Trp Leu Pro

CAA ATT GTG AGA CTA AAG GAT ACG AGA TCA AGC TTA TCG ATA CCG TCG      960
Gln Ile Val Arg Leu Lys Asp Thr Arg Ser Ser Leu Ser Ile Pro Ser

ACC TCG A                                                           967
Thr Ser
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 322 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Ala Lys Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe
  1               5                  10                  15
Ser Ser Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly
            20                  25                  30
Gly Asn Cys Leu Leu Asn Ile Pro Lys Pro Asp Glu Ala Tyr Ser Ala
        35                  40                  45
Pro Ser Cys Gly Asn Lys Leu Val Asp Ala Gly Glu Glu Cys Asp Cys
    50                  55                  60
Gly Thr Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys Glu Gly Ser Thr
65                  70                  75                  80
Cys Lys Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly Asp Cys Cys Lys
                85                  90                  95
Asp Cys Arg Phe Leu Pro Gly Gly Thr Leu Cys Arg Gly Lys Thr Ser
            100                 105                 110
Glu Cys Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser Gln Phe Cys Gln
        115                 120                 125
Pro Asp Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln Asn Asn Lys Ala

    130                 135                 140
Tyr Cys Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala Gln Cys Gln Val
145                 150                 155                 160
Ile Phe Gly Ser Lys Ala Lys Ala Ala Pro Lys Asp Cys Phe Ile Glu
                165                 170                 175
Val Asn Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Asn
            180                 185                 190
Glu Tyr Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln
        195                 200                 205
Cys Glu Asn Val Gln Glu Ile Pro Val Phe Gly Ile Val Pro Ala Ile
    210                 215                 220
Ile Gln Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln
225                 230                 235                 240
Leu Gly Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys
                245                 250                 255
Cys Gly Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asp Ala Ser
            260                 265                 270
Val Leu Asn Tyr Asp Cys Asp Val Gln Lys Lys Cys His Gly His Gly
        275                 280                 285
Val Cys Asn Ser Asn Lys Asn Cys His Cys Glu Asn Gly Trp Leu Pro
    290                 295                 300
Gln Ile Val Arg Leu Lys Asp Thr Arg Ser Ser Leu Ser Ile Pro Ser
305                 310                 315                 320
Thr Ser
```

SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2848 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE:JM109(pMel α-25C)
JM109 (pMel α-26N)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
GGG GAC CTC TGG ATC CCA GTG AAG AGC TTC GAC TCC AAG AAT CAT CCA      48
Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His Pro

GAA GTG CTG AAT ATT CGA CTA CAA CGG GAA AGC AAA GAA CTG ATC ATA      96
Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile Ile

AAT CTG GAA AGA AAT GAA GGT CTC ATT GCC AGC AGT TTC ACG GAA ACC     144
Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser Ser Phe Thr Glu Thr

CAC TAT CTG CAA GAC GGT ACT GAT GTC TCC CTC GCT CGA AAT TAC ACG     192
His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr Thr

GGT CAC TGT TAC TAC CAT GGA CAT GTA CGG GGA TAT TCT GAT TCA GCA     240
Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser Ala
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GTC AGT CTC AGC ACG TGT TCT GGT CTC AGG GGA CTT ATT GGG TTT GAA      288
Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Gly Phe Glu

AAT GAA AGC TAT GTC TTA GAA CCA ATG AAA AGT GCA ACC AAC AGA TAC      336
Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg Tyr

AAA CTC TTC CCA GCG AAG AAG CTG AAA AGC GTC CGG GGA TCA TGT GGA      384
Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg Gly Ser Cys Gly

TCA CAT CAC AAC ACA CCA AAC CTC GCT GCA AAG AAT GTG TTT CCA CCA      432
Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro Pro

CCC TCT CAG ACA TGG GCA AGA AGG CAT AAA AGA GAG ACC CTC AAG GCA      480
Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys Ala

ACT AAG TAT GTG GAG CTG GTG ATC GTG GCA GAC AAC CGA GAG TTT CAG      528
Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln

AGG CAA GGA AAA GAT CTG GAA AAA GTT AAG CAG CGA TTA ATA GAG ATT      576
Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile

GCT AAT CAC GTT GAC AAG TTT TAC AGA CCA CTG AAC ATT CGG ATC GTG      624
Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val

TTG GTA GGC GTG GAA GTG TGG AAT GAC ATG GAC AAA TGC TCT GTA AGT      672
Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val Ser

CAG GAC CCA TTC ACC AGC CTC CAT GAA TTT CTG GAC TGG AGG AAG ATG      720
Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys Met

AAG CTT CTA CCT CGC AAA TCC CAT GAC AAT GCG CAG CTT GTC AGT GGG      768
Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser Gly

GTT TAT TTC CAA GGG ACC ACC ATC GGC ATG GCC CCA ATC ATG AGC ATG      816
Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met

TGC ACG GCA GAC CAG TCT GGG GGA ATT GTC ATG GAC CAT TCA GAC AAT      864
Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp Asn

CCC CTT GGT GCA GCC GTG ACC CTG GCA CAT GAG CTG GGC CAC AAT TTC      912
Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe

GGG ATG AAT CAT GAC ACA CTG GAC AGG GGC TGT AGC TGT CAA ATG GCG      960
Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met Ala

GTT GAG AAA GGA GGC TGC ATC ATG AAC GCT TCC ACC GGG TAC CCA TTT     1008
Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro Phe

CCC ATG GTG TTC AGC AGT TGC AGC AGG AAG GAC TTG GAG ACC AGC CTG     1056
Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser Leu

GAG AAA GGA ATG GGG GTG TGC CTG TTT AAC CTG CCG GAA GTC AGG GAG     1104
Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg Glu
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TCT TTC GGG GGC CAG AAG TGT GGG AAC AGA TTT GTG GAA GAA GGA GAG     1152
Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly Glu

GAG TGT GAC TGT GGG GAG CCA GAG GAA TGT ATG AAT CGC TGC TGC AAT     1200
Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys Asn

GCC ACC ACC TGT ACC CTG AAG CCG GAC GCT GTG TGC GCA CAT GGG CTG     1248
Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly Leu

TGC TGT GAA GAC TGC CAG CTG AAG CCT GCA GGA ACA GCG TGC AGG GAC     1296
Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg Asp

TCC AGC AAC TCC TGT GAC CTC CCA GAG TTC TGC ACA GGG GCC AGC CCT     1344
Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser Pro

CAC TGC CCA GCC AAC GTG TAC CTG CAC GAT GGG CAC TCA TGT CAG GAT     1392
His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln Asp

GTG GAC GGC TAC TGC TAC AAT GGC ATC TGC CAG ACT CAC GAG CAG CAG     1440
Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln Gln

TGT GTC ACG CTC TGG GGA CCA GGT GCT AAA CCT GCC CCT GGG ATC TGC     1488
Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile Cys

TTT GAG AGA GTC AAT TCT GCA GGT GAT CCT TAT GGC AAC TGT GGC AAA     1536
Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly Lys

GTC TCG AAG AGT TCC TTT GCC AAA TGC GAG ATG AGA GAT GCT AAA TGT     1584
Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys Cys

GGA AAA ATC CAG TGT CAA GGA GGT GCC AGC CGG CCA GTC ATT GGT ACC     1632
Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly Thr

AAT GCC GTT TCC ATA GAA ACA AAC ATC CCC CTG CAG CAA GGA GGC CGG     1680
Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly Arg

ATT CTG TGC CGG GGG ACC CAC GTG TAC TTG GGC GAT GAC ATG CCG GAC     1728
Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro Asp

CCA GGG CTT GTG CTT GCA GGC ACA AAG TGT GCA GAT GGA AAA ATC TGC     1776
Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile Cys

CTG AAT CGT CAA TGT CAA AAT ATT AGT GTC TTT GGG GTT CAC GAG TGT     1824
Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu Cys

GCA ATG CAG TGC CAC GGC AGA GGG GTG TGC AAC AAC AGG AAG AAC TGC     1872
Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn Cys

CAC TGC GAG GCC CAC TGG GCA CCT CCC TTC TGT GAC AAG TTT GGC TTT     1920
His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly Phe

GGA GGA AGC ACA GAC AGC GGC CCC ATC CGG CAA GCA GAA GCA AGG CAG     1968
Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Glu Ala Arg Gln

GAA GCT GCA GAG TCC AAC AGG GAG CGC GGC CAG GGC CAG GAG CCC GTG     2016
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Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly Gln Glu Pro Val

GGA TCG CAG GAG CAT GCG TCT ACT GCC TCA CTG ACA CTC ATC TGA          2061
Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr Leu Ile  *

GCCCTCCCAT GACATGGAGA CCGTGACCAG TGCTGCTGCA GAGGAGGTCA CGCGTCCCCA   2121
AGGCCTCCTG TGACTGGCAG CATTGACTCT GTGGCTTTGC CATCGTTTCC ATGACAACAG   2181
ACACAACACA GTTCTCGGGG CTCAGGAGGG GAAGTCCAGC CTACCAGGCA CGTCTGCAGA   2241
AACAGTGCAA GGAAGGGCAG CGACTTCCTG GTTGAGCTTC TGCTAAAACA TGGACATGCT   2301
TCAGTGCTGC TCCTGAGAGA GTAGCAGGTT ACCACTCTGG CAGGCCCCAG CCCTGCAGCA   2361
AGGAGGAAGA GGACTCAAAA GTCTGGCCTT TCACTGAGCC CCCACAGCAG TGGGGGAGAA   2421
GCAAGGGTTG GGCCCAGTGT CCCCTTTCCC CAGTGACACC TCAGCCTTGG CAGCCCTGAT   2481
GACTGGTCTC TGGCTGCAAC TTAATGCTCT GATATGGCTT TTAGCATTTA TTATATGAAA   2541
ATAGCAGGGT TTTAGTTTTT AATTTATCAG AGACCCTGCC ACCCATTCCA TCTCCATCCA   2601
AGCAAACTGA ATGGCATTGA AACAAACTGG AGAAGAAGGT AGGAGAAAGG GCGGTGAACT   2661
CTGGCTCTTT GCTGTGGACA TGCGTGACCA GCAGTACTCA GGTTTGAGGG TTTGCAGAAA   2721
GCCAGGGAAC CCACAGAGTC ACCAACCCTT CATTTAACAA GTAAGAATGT TAAAAAGTGA   2781
AAACAATGTA AGAGCCTAAC TCCATCCCCC GTGGCCATTA CTGCATAAAA TAGAGTGCAT   2841
CCCGCCC                                                            2848
```

SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 686 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His Pro

Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile Ile

Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser Ser Phe Thr Glu Thr

His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr Thr

Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser Ala

Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Gly Phe Glu

Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg Tyr

Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg Gly Ser Cys Gly

Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro Pro

Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys Ala
-1 1

Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln

Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile

Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val

Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val Ser
Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys Met
Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser Gly
Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met
Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp Asn
Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe
Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met Ala
Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro Phe
Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser Leu
Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg Glu
Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly Glu
Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys Asn
Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly Leu
Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg Asp
Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser Pro
His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln Asp
Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln Gln
Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile Cys
Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly Lys
Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys Cys
Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly Thr
Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly Arg
Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro Asp
Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile Cys
Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu Cys
Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn Cys
His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly Phe

Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Glu Ala Arg Gln

Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly Gln Glu Pro Val

Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr Leu Ile

SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 394 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
GGG GAA GAG TGT GAT TGT GGA GAA GAA GAG GAA TGT AAC AAC CCC TGC      48
Gly Glu Glu Cys Asp Cys Gly Glu Glu Glu Glu Cys Asn Asn Pro Cys

TGC AAT GCC TCT AAT TGT ACC CTG AGG CCG GGG GCG GAG TGT GCT CAC      96
Cys Asn Ala Ser Asn Cys Thr Leu Arg Pro Gly Ala Glu Cys Ala His

GGC TCC TGC TGC CAC CAG TGT AAG CTG TTG GCT CCT GGG ACC CTG TGC     144
Gly Ser Cys Cys His Gln Cys Lys Leu Leu Ala Pro Gly Thr Leu Cys

CGC GAG CAG GCC AGG CAG TGT GAC CTC CCG GAG TTC TGT ACG GGC AAG     192
Arg Glu Gln Ala Arg Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys

TCT CCC CAC TGC CCT ACC AAC TTC TAC CAG ATG GAT GGT ACC CCC TGT     240
Ser Pro His Cys Pro Thr Asn Phe Tyr Gln Met Asp Gly Thr Pro Cys

GAG GGC GGC CAG GCC TAC TGC TAC AAC GGC ATG TGC CTC ACC TAC CAG     288
Glu Gly Gly Gln Ala Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln

GAG CAG TGC CAG CAG CTG TGG GGA CCC GGA GCC CGA CCT GCC CCT GAC     336
Glu Gln Cys Gln Gln Leu Trp Gly Pro Gly Ala Arg Pro Ala Pro Asp

CTC TGC TTC GAG AAG GTG AAT GTG GCA GGA GAC ACC TTT GGA AAC TGT     384
Leu Cys Phe Glu Lys Val Asn Val Ala Gly Asp Thr Phe Gly Asn Cys

GGA AAG GAC A                                                      394
Gly Lys Asp
```

SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 131 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Gly Glu Glu Cys Asp Cys Gly Glu Glu Glu Glu Cys Asn Asn Pro Cys
 1               5                  10                  15
Cys Asn Ala Ser Asn Cys Thr Leu Arg Pro Gly Ala Glu Cys Ala His
            20                  25                  30
Gly Ser Cys Cys His Gln Cys Lys Leu Leu Ala Pro Gly Thr Leu Cys
        35                  40                  45
Arg Glu Gln Ala Arg Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys
    50                  55                  60
Ser Pro His Cys Pro Thr Asn Phe Tyr Gln Met Asp Gly Thr Pro Cys
65                  70                  75                  80
Glu Gly Gly Gln Ala Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln
                85                  90                  95
Glu Gln Cys Gln Gln Leu Trp Gly Pro Gly Ala Arg Pro Ala Pro Asp
            100                 105                 110
Leu Cys Phe Glu Lys Val Asn Val Ala Gly Asp Thr Phe Gly Asn Cys
        115                 120                 125
Gly Lys Asp
    130
```

SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1183 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
C GGA GCT GCC ACT GGG CAC CCC TTT CCC AAA GTG TTC AAT GGA TGC          46
  Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys

AAC AGG AGG GAG CTG GAC AGG TAT CTG CAG TCA GGT GGT GGA ATG TGT        94
Asn Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys

CTC TCC AAC ATG CCA GAC ACC AGG ATG TTG TAT GGA GGC CGG AGG TGT       142
Leu Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys

GGG AAC GGG TAT CTG GAA GAT GGG GAA GAG TGT GAC TGT GGA GAA GAA       190
Gly Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu

GAG GAA TGT AAC AAC CCC TGC TGC AAT GCC TCT AAT TGT ACC CTG AGG       238
Glu Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg

CCG GGG GCG GAG TGT GCT CAC GGC TCC TGC TGC CAC CAG TGT AAG CTG       286
Pro Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu

TTG GCT CCT GGG ACC CTG TGC CGC GAG CAG GCC AGG CAG TGT GAC CTC       334
Leu Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu

CCG GAG TTC TGT ACG GGC AAG TCT CCC CAC TGC CCT ACC AAC TTC TAC       382
Pro Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr
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CAG ATG GAT GGT ACC CCC TGT GAG GGC GGC CAG GCC TAC TGC TAC AAC      430
Gln Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn

GGC ATG TGC CTC ACC TAC CAG GAG CAG TGC CAG CAG CTG TGG GGA CCC      478
Gly Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln Gln Leu Trp Gly Pro

GGA GCC CGA CCT GCC CCT GAC CTC TGC TTC GAG AAG GTG AAT GTG GCA      526
Gly Ala Arg Pro Ala Pro Asp Leu Cys Phe Glu Lys Val Asn Val Ala

GGA GAC ACC TTT GGA AAC TGT GGA AAG GAC ATG AAT GGT GAA CAC AGG      574
Gly Asp Thr Phe Gly Asn Cys Gly Lys Asp Met Asn Gly Glu His Arg

AAG TGC AAC ATG AGA GAT GCG AAG TGT GGG AAG ATC CAG TGT CAG AGC      622
Lys Cys Asn Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Ser

TCT GAG GCC CGG CCC CTG GAG TCC AAC GCG GTG CCC ATT GAC ACC ACT      670
Ser Glu Ala Arg Pro Leu Glu Ser Asn Ala Val Pro Ile Asp Thr Thr

ATC ATC ATG AAT GGG AGG CAG ATC CAG TGC CGG GGC ACC CAC GTC TAC      718
Ile Ile Met Asn Gly Arg Gln Ile Gln Cys Arg Gly Thr His Val Tyr

CGA GGT CCT GAG GAG GAG GGT GAC ATG CTG GAC CCA GGG CTG GTG ATG      766
Arg Gly Pro Glu Glu Glu Gly Asp Met Leu Asp Pro Gly Leu Val Met

ACT GGA ACC AAG TGT GGC TAC AAC CAT ATT TGC CTT GAG GGG CAG TGC      814
Thr Gly Thr Lys Cys Gly Tyr Asn His Ile Cys Leu Glu Gly Gln Cys

AGG AAC ACC TCC TTC TTT GAA ACT GAA GGC TGT GGG AAG AAG TGC AAT      862
Arg Asn Thr Ser Phe Phe Glu Thr Glu Gly Cys Gly Lys Lys Cys Asn

GGC CAT GGG GTC TGT AAC AAC AAC CAG AAC TGC CAC TGC CTG CCG GGC      910
Gly His Gly Val Cys Asn Asn Asn Gln Asn Cys His Cys Leu Pro Gly

TGG GCC CCG CCC TTC TGC AAC ACA CCG GGC CAC GGG GGC AGT ATC GAC      958
Trp Ala Pro Pro Phe Cys Asn Thr Pro Gly His Gly Gly Ser Ile Asp

AGT GGG CCT ATG CCC CCT GAG AGT GTG GGT CCT GTG GTA GCT GGA GTG     1006
Ser Gly Pro Met Pro Pro Glu Ser Val Gly Pro Val Val Ala Gly Val

TTG GTG GCC ATC TTG GTG CTG GCG GTC CTC ATG CTG ATG TAC TAC TGC     1054
Leu Val Ala Ile Leu Val Leu Ala Val Leu Met Leu Met Tyr Tyr Cys

TGC AGA CAG AAC AAC AAA CTA GGC CAA CTC AAG CCC TCA GCT CTC CCT     1102
Cys Arg Gln Asn Asn Lys Leu Gly Gln Leu Lys Pro Ser Ala Leu Pro

TCC AAG CTG AGG CAA CAG TTC AGT TGT CCC TTC AGG GTT TCT CAG AAC     1150
Ser Lys Leu Arg Gln Gln Phe Ser Cys Pro Phe Arg Val Ser Gln Asn

AGC GGG ACT GGT CAT GCC AAC CCA ACT TTC AAG                        1183
Ser Gly Thr Gly His Ala Asn Pro Thr Phe Lys
```

SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 394 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys Asn
 1               5                  10                  15
Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys Leu
            20                  25                  30
Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys Gly
        35                  40                  45
Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu Glu
    50                  55                  60
Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg Pro
65                  70                  75                  80
Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu Leu
                85                  90                  95
Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu Pro
            100                 105                 110
Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr Gln
        115                 120                 125
Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn Gly
    130                 135                 140
Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln Gln Leu Trp Gly Pro Gly
145                 150                 155                 160
Ala Arg Pro Ala Pro Asp Leu Cys Phe Glu Lys Val Asn Val Ala Gly
                165                 170                 175
Asp Thr Phe Gly Asn Cys Gly Lys Asp Met Asn Gly Glu His Arg Lys
            180                 185                 190
Cys Asn Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Ser Ser
        195                 200                 205
Glu Ala Arg Pro Leu Glu Ser Asn Ala Val Pro Ile Asp Thr Thr Ile
    210                 215                 220
Ile Met Asn Gly Arg Gln Ile Gln Cys Arg Gly Thr His Val Tyr Arg
225                 230                 235                 240
Gly Pro Glu Glu Glu Gly Asp Met Leu Asp Pro Gly Leu Val Met Thr
                245                 250                 255
Gly Thr Lys Cys Gly Tyr Asn His Ile Cys Leu Glu Gly Gln Cys Arg
            260                 265                 270
Asn Thr Ser Phe Phe Glu Thr Glu Gly Cys Gly Lys Lys Cys Asn Gly
        275                 280                 285
His Gly Val Cys Asn Asn Asn Gln Asn Cys His Cys Leu Pro Gly Trp
    290                 295                 300
Ala Pro Pro Phe Cys Asn Thr Pro Gly His Gly Gly Ser Ile Asp Ser
305                 310                 315                 320
Gly Pro Met Pro Pro Glu Ser Val Gly Pro Val Val Ala Gly Val Leu
                325                 330                 335
Val Ala Ile Leu Val Leu Ala Val Leu Met Leu Met Tyr Tyr Cys Cys
            340                 345                 350
Arg Gln Asn Asn Lys Leu Gly Gln Leu Lys Pro Ser Ala Leu Pro Ser
        355                 360                 365
Lys Leu Arg Gln Gln Phe Ser Cys Pro Phe Arg Val Ser Gln Asn Ser
    370                 375                 380
Gly Thr Gly His Ala Asn Pro Thr Phe Lys
385                 390
```

SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 624 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE:

(B) CLONE:CLONE TM

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
GC ACA AAG TGT GCA GAT GGA AAA ATC TGC CTG AAT CGT CAA TGT CAA        47
   Thr Lys Cys Ala Asp Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln

AAT ATT AGT GTC TTT GGG GTT CAC GAG TGT GCA ATG CAG TGC CAC GGC        95
Asn Ile Ser Val Phe Gly Val His Glu Cys Ala Met Gln Cys His Gly

AGA GGG GTG TGC AAC AAC AGG AAG AAC TGC CAC TGC GAG GCC CAC TGG       143
Arg Gly Val Cys Asn Asn Arg Lys Asn Cys His Cys Glu Ala His Trp

GCA CCT CCC TTC TGT GAC AAG TTT GGC TTT GGA GGA AGC ACA GAC AGC       191
Ala Pro Pro Phe Cys Asp Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser

GGC CCC ATC CGG CAA GCA GAT AAC CAA GGT TTA ACC ATA GGA ATT CTG       239
Gly Pro Ile Arg Gln Ala Asp Asn Gln Gly Leu Thr Ile Gly Ile Leu

GTG ACC ATC CTG TGT CTT CTT GCT GCC GGA TTT GTG GTT TAT CTC AAA       287
Val Thr Ile Leu Cys Leu Leu Ala Ala Gly Phe Val Val Tyr Leu Lys

AGG AAG ACC TTG ATA CGA CTG CTG TTT ACA AAT AAG AAG ACC ACC ATT       335
Arg Lys Thr Leu Ile Arg Leu Leu Phe Thr Asn Lys Lys Thr Thr Ile

GAA AAA CTA AGG TGT GTG CGC CCT TCC CGG CCA CCC CGT GGC TTC CAA       383
Glu Lys Leu Arg Cys Val Arg Pro Ser Arg Pro Pro Arg Gly Phe Gln

CCC TGT CAG GCT CAC CTC GGC CAC CTT GGA AAA GGC CTG ATG AGG AAG       431
Pro Cys Gln Ala His Leu Gly His Leu Gly Lys Gly Leu Met Arg Lys

CCG CCA GAT TCC TAC CCA CCG AAG GAC AAT CCC AGG AGA TTG CTG CAG       479
Pro Pro Asp Ser Tyr Pro Pro Lys Asp Asn Pro Arg Arg Leu Leu Gln

TGT CAG AAT GTT GAC ATC AGC AGA CCC CTC AAC GGC CTG AAT GTC CCT       527
Cys Gln Asn Val Asp Ile Ser Arg Pro Leu Asn Gly Leu Asn Val Pro

CAG CCC CAG TCA ACT CAG CGA GTG CTT CCT CCC CTC CAC CGG GCT CCA       575
Gln Pro Gln Ser Thr Gln Arg Val Leu Pro Pro Leu His Arg Ala Pro

CGT GCA CCT AGC GTC CCT GCC AGA CCC CTG CCA GCC AAG CCT GCA CTT       623
Arg Ala Pro Ser Val Pro Ala Arg Pro Leu Pro Ala Lys Pro Ala Leu

A                                                                    624
```

SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 207 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Thr Lys Cys Ala Asp Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn
 1               5                  10                  15
Ile Ser Val Phe Gly Val His Glu Cys Ala Met Gln Cys His Gly Arg
            20                  25                  30
Gly Val Cys Asn Asn Arg Lys Asn Cys His Cys Glu Ala His Trp Ala
        35                  40                  45
Pro Pro Phe Cys Asp Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly
    50                  55                  60
Pro Ile Arg Gln Ala Asp Asn Gln Gly Leu Thr Ile Gly Ile Leu Val
65                  70                  75                  80
Thr Ile Leu Cys Leu Leu Ala Ala Gly Phe Val Val Tyr Leu Lys Arg
                85                  90                  95
Lys Thr Leu Ile Arg Leu Leu Phe Thr Asn Lys Lys Thr Thr Ile Glu
            100                 105                 110
Lys Leu Arg Cys Val Arg Pro Ser Arg Pro Pro Arg Gly Phe Gln Pro
        115                 120                 125
Cys Gln Ala His Leu Gly His Leu Gly Lys Gly Leu Met Arg Lys Pro
    130                 135                 140
Pro Asp Ser Tyr Pro Pro Lys Asp Asn Pro Arg Arg Leu Leu Gln Cys
145                 150                 155                 160
Gln Asn Val Asp Ile Ser Arg Pro Leu Asn Gly Leu Asn Val Pro Gln
                165                 170                 175
Pro Gln Ser Thr Gln Arg Val Leu Pro Pro Leu His Arg Ala Pro Arg
            180                 185                 190
Ala Pro Ser Val Pro Ala Arg Pro Leu Pro Ala Lys Pro Ala Leu
        195                 200                 205
```

SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2669 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE:JM109 (pMel β-24C)
JM109 (pMel β-24N)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
C GGA GCT GCC ACT GGG CAC CCC TTT CCC AAA GTG TTC AAT GGA TGC          46
  Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys

AAC AGG AGG GAG CTG GAC AGG TAT CTG CAG TCA GGT GGT GGA ATG TGT        94
```

```
Asn Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys

CTC TCC AAC ATG CCA GAC ACC AGG ATG TTG TAT GGA GGC CGG AGG TGT      142
Leu Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys

GGG AAC GGG TAT CTG GAA GAT GGG GAA GAG TGT GAC TGT GGA GAA GAA      190
Gly Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu

GAG GAA TGT AAC AAC CCC TGC TGC AAT GCC TCT AAT TGT ACC CTG AGG      238
Glu Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg

CCG GGG GCG GAG TGT GCT CAC GGC TCC TGC TGC CAC CAG TGT AAG CTG      286
Pro Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu

TTG GCT CCT GGG ACC CTG TGC CGC GAG CAG GCC AGG CAG TGT GAC CTC      334
Leu Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu

CCG GAG TTC TGT ACG GGC AAG TCT CCC CAC TGC CCT ACC AAC TTC TAC      382
Pro Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr

CAG ATG GAT GGT ACC CCC TGT GAG GGC GGC CAG GCC TAC TGC TAC AAC      430
Gln Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn

GGC ATG TGC CTC ACC TAC CAG GAG CAG TGC CAG CAG CTG TGG GGA CCC      478
Gly Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln Gln Leu Trp Gly Pro

GGA GCC CGA CCT GCC CCT GAC CTC TGC TTC GAG AAG GTG AAT GTG GCA      526
Gly Ala Arg Pro Ala Pro Asp Leu Cys Phe Glu Lys Val Asn Val Ala

GGA GAC ACC TTT GGA AAC TGT GGA AAG GAC ATG AAT GGT GAA CAC AGG      574
Gly Asp Thr Phe Gly Asn Cys Gly Lys Asp Met Asn Gly Glu His Arg

AAG TGC AAC ATG AGA GAT GCG AAG TGT GGG AAG ATC CAG TGT CAG AGC      622
Lys Cys Asn Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Ser

TCT GAG GCC CGG CCC CTG GAG TCC AAC GCG GTG CCC ATT GAC ACC ACT      670
Ser Glu Ala Arg Pro Leu Glu Ser Asn Ala Val Pro Ile Asp Thr Thr

ATC ATC ATG AAT GGG AGG CAG ATC CAG TGC CGG GGC ACC CAC GTC TAC      718
Ile Ile Met Asn Gly Arg Gln Ile Gln Cys Arg Gly Thr His Val Tyr

CGA GGT CCT GAG GAG GAG GGT GAC ATG CTG GAC CCA GGG CTG GTG ATG      766
Arg Gly Pro Glu Glu Glu Gly Asp Met Leu Asp Pro Gly Leu Val Met

ACT GGA ACC AAG TGT GGC TAC AAC CAT ATT TGC CTT GAG GGG CAG TGC      814
Thr Gly Thr Lys Cys Gly Tyr Asn His Ile Cys Leu Glu Gly Gln Cys

AGG AAC ACC TCC TTC TTT GAA ACT GAA GGC TGT GGG AAG AAG TGC AAT      862
Arg Asn Thr Ser Phe Phe Glu Thr Glu Gly Cys Gly Lys Lys Cys Asn

GGC CAT GGG GTC TGT AAC AAC AAC CAG AAC TGC CAC TGC CTG CCG GGC      910
Gly His Gly Val Cys Asn Asn Asn Gln Asn Cys His Cys Leu Pro Gly

TGG GCC CCG CCC TTC TGC AAC ACA CCG GGC CAC GGG GGC AGT ATC GAC      958
Trp Ala Pro Pro Phe Cys Asn Thr Pro Gly His Gly Gly Ser Ile Asp
```

```
AGT GGG CCT ATG CCC CCT GAG AGT GTG GGT CCT GTG GTA GCT GGA GTG      1006
Ser Gly Pro Met Pro Pro Glu Ser Val Gly Pro Val Val Ala Gly Val

TTG GTG GCC ATC TTG GTG CTG GCG GTC CTC ATG CTG ATG TAC TAC TGC      1054
Leu Val Ala Ile Leu Val Leu Ala Val Leu Met Leu Met Tyr Tyr Cys

TGC AGA CAG AAC AAC AAA CTA GGC CAA CTC AAG CCC TCA GCT CTC CCT      1102
Cys Arg Gln Asn Asn Lys Leu Gly Gln Leu Lys Pro Ser Ala Leu Pro

TCC AAG CTG AGG CAA CAG TTC AGT TGT CCC TTC AGG GTT TCT CAG AAC      1150
Ser Lys Leu Arg Gln Gln Phe Ser Cys Pro Phe Arg Val Ser Gln Asn

AGC GGG ACT GGT CAT GCC AAC CCA ACT TTC AAG CCG GAA TTC CGG GCC      1198
Ser Gly Thr Gly His Ala Asn Pro Thr Phe Lys Pro Glu Phe Arg Ala

CCC CAC AGC CCA CAC CAC CAT GAC AAG GGC CAC CAA TTC CAC GGC CAC      1246
Pro His Ser Pro His His His Asp Lys Gly His Gln Phe His Gly His

ACC CTC CTC CAC TCT GGG GAC GAC CCG GAT CCT CAC TGA GCTGACCACA       1295
Thr Leu Leu His Ser Gly Asp Asp Pro Asp Pro His  *

ACAGCCACTA CAACTGCAGC CACTGGATCC ACGGCCACCC TGTCCTCCAC CCCAGGGACC    1355
ACCTGGATCC TCACAGAGCC GAGCACTATA GCCACCGTGA TGGTGCCCAC CGGTTCCACG    1415
GCCACCGCCT CCTCCACTCT GGGAACAGCT CACACCCCCA AAGTGGTGAC CACCATGGCC    1475
ACTATGCCCA CAGCCACTGC CTCCACGGTT CCCAGCTCGT CCACCGTGGG GACCACCCGC    1535
ACCCCTGCAG TGCTCCCCAG CAGCCTGCCA ACCTTCAGCG TGTCCACTGT GTCCTCCTCA    1595
GTCCTCACCA CCCTGAGACC CACTGGCTTC CCCAGCTCCC ACTTCTCTAC TCCCTGCTTC    1655
TGCAGGGCAT TTGGACAGTT TTTCTCGCCC GGGGAAGTCA TCTACAATAA GACCGACCGA    1715
GCCGGCTGCC ATTTCTACGC AGTGTGCAAT CAGCACTGTG ACATTGACCG CTTCCAGGGC    1775
GCCTGTCCCA CCTCCCCACC GCCAGTGTCC TCCGCCCCGC TGTCCTCGCC CTCCCCTGCC    1835
CCTGGCTGTG ACAATGCCAT CCCTCTCCGG CAGGTGAATG AGACCTGGAC CCTGGAGAAC    1895
TGCACGGTGG CCAGGTGCGT GGGTGACAAC CGTGTCGTCC TGCTGGACCC AAAGCCTGTG    1955
GCCAACGTCA CCTGCGTGAA CAAGCACCTG CCCATCAAAG TGTCGGACCC GAGCCAGCCC    2015
TGTGACTTCC ACTATGAGTG CGAGTGCATC TGCAGCATGT GGGGCGGCTC CCACTATTCC    2075
ACCTTTGACG GCACCTCTTA CACCTTCCGG GGCAACTGCA CCTATGTCCT CATGAGAGAG    2135
ATCCATGCAC GCTTTGGGAA TCTCAGCCTC TACCTGGACA ACCACTACTG CACGGCCTCT    2195
GCCACTGCCG CTGCCGCCCG CTGCCCCCGC GCCCTCAGCA TCCACTACAA GTCCATGGAT    2255
ATCGTCCTCA CTGTCACCAT GGTGCATGGG AAGGAGGAGG GCCTGATCCT GTTTGACCAA    2315
ATTCCGGTGA GCAGCGGTTT CAGCAAGAAC GGCGTGCTTG TGTCTGTGCT GGGGACCACC    2375
ACCATGCGTG TGGACATTCC TGCCCTGGGC GTGAGCGTCA CCTTCAATGG CCAAGTCTTC    2435
CAGGCCCGGC TGCCCTACAG CCTCTTCCAC AACAACACCG AGGGCCAGTG CGGCACCTGC    2495
ACCAACAACC AGAGGGACGA CTGTCTCCAG CGGGACGGAA CCACTGCCGC CAGTTGCAAG    2555
GACATGGCCA AGACGTGGCT GGTCCCCGAC AGCAGAAAGG ATGGCTGCTG GGCCCCGACT    2615
GGCACACCCC CCACTGCCAG CCCCGCAGCC CCGGTGTCTA GCACACCCAC CCCG           2669
```

SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 427 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys Asn
 1               5                  10                  15
Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys Leu
            20                  25                  30
Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys Gly
        35                  40                  45
Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu Glu
    50                  55                  60
Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg Pro
65                  70                  75                  80
Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu Leu
                85                  90                  95
Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu Pro
            100                 105                 110
Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr Gln
        115                 120                 125
Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn Gly
    130                 135                 140
Met Cys Leu Thr Tyr Gln Glu Gln Cys Gln Gln Leu Trp Gly Pro Gly
145                 150                 155                 160
Ala Arg Pro Ala Pro Asp Leu Cys Phe Glu Lys Val Asn Val Ala Gly
                165                 170                 175
Asp Thr Phe Gly Asn Cys Gly Lys Asp Met Asn Gly Glu His Arg Lys
            180                 185                 190
Cys Asn Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Ser Ser
        195                 200                 205
Glu Ala Arg Pro Leu Glu Ser Asn Ala Val Pro Ile Asp Thr Thr Ile
    210                 215                 220
Ile Met Asn Gly Arg Gln Ile Gln Cys Arg Gly Thr His Val Tyr Arg
225                 230                 235                 240
Gly Pro Glu Glu Glu Gly Asp Met Leu Asp Pro Gly Leu Val Met Thr
                245                 250                 255
Gly Thr Lys Cys Gly Tyr Asn His Ile Cys Leu Glu Gly Gln Cys Arg
            260                 265                 270
Asn Thr Ser Phe Phe Glu Thr Glu Gly Cys Gly Lys Lys Cys Asn Gly
        275                 280                 285
His Gly Val Cys Asn Asn Asn Gln Asn Cys His Cys Leu Pro Gly Trp
    290                 295                 300
Ala Pro Pro Phe Cys Asn Thr Pro Gly His Gly Gly Ser Ile Asp Ser
305                 310                 315                 320
Gly Pro Met Pro Pro Glu Ser Val Gly Pro Val Val Ala Gly Val Leu
                325                 330                 335
Val Ala Ile Leu Val Leu Ala Val Leu Met Leu Met Tyr Tyr Cys Cys
            340                 345                 350
Arg Gln Asn Asn Lys Leu Gly Gln Leu Lys Pro Ser Ala Leu Pro Ser
        355                 360                 365
Lys Leu Arg Gln Gln Phe Ser Cys Pro Phe Arg Val Ser Gln Asn Ser
    370                 375                 380
Gly Thr Gly His Ala Asn Pro Thr Phe Lys Pro Glu Phe Arg Ala Pro
385                 390                 395                 400
His Ser Pro His His His Asp Lys Gly His Gln Phe His Gly His Thr
                405                 410                 415
Leu Leu His Ser Gly Asp Asp Pro Asp Pro His
            420                 425
```

SEQ ID N0:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1483 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE:JM109 (pMel α-25C)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
GAT GGG CAC TCA TGT CAG GAT GTG GAC GGC TAC TGC TAC AAT GGC ATC      48
Asp Gly His Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile

AAA CCT GCC CCT GGG ATC TGC TTT GAG AGA GTC AAT TCT GCA GGT GAT     144
Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp

CCT TAT GGC AAC TGT GGC AAA GTC TCG AAG AGT TCC TTT GCC AAA TGC     192
Pro Tyr Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys

GAG ATG AGA GAT GCT AAA TGT GGA AAA ATC CAG TGT CAA GGA GGT GCC     240
Glu Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala

AGC CGG CCA GTC ATT GGT ACC AAT GCC GTT TCC ATA GAA ACA AAC ATC     288
Ser Arg Pro Val Ile Gly Thr Asn Ala Val Ser Ile Glu Thr Asn Ile

CCC CTG CAG CAA GGA GGC CGG ATT CTG TGC CGG GGG ACC CAC GTG TAC     336
Pro Leu Gln Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr

TTG GGC GAT GAC ATG CCG GAC CCA GGG CTT GTG CTT GCA GGC ACA AAG     384
Leu Gly Asp Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys

TGT GCA GAT GGA AAA ATC TGC CTG AAT CGT CAA TGT CAA AAT ATT AGT     432
Cys Ala Asp Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser

GTC TTT GGG GTT CAC GAG TGT GCA ATG CAG TGC CAC GGC AGA GGG GTG     480
Val Phe Gly Val His Glu Cys Ala Met Gln Cys His Gly Arg Gly Val

TGC AAC AAC AGG AAG AAC TGC CAC TGC GAG GCC CAC TGG GCA CCT CCC     528
Cys Asn Asn Arg Lys Asn Cys His Cys Glu Ala His Trp Ala Pro Pro

TTC TGT GAC AAG TTT GGC TTT GGA GGA AGC ACA GAC AGC GGC CCC ATC     576
Phe Cys Asp Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile

CGG CAA GCA GAA GCA AGG CAG GAA GCT GCA GAG TCC AAC AGG GAG CGC     624
Arg Gln Ala Glu Ala Arg Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg

GGC CAG GGC CAG GAG CCC GTG GGA TCG CAG GAG CAT GCG TCT ACT GCC     672
Gly Gln Gly Gln Glu Pro Val Gly Ser Gln Glu His Ala Ser Thr Ala

TCA CTG ACA CTC ATC TGA GCCCTCCCAT GACATGGAGA CCGTGACCAG           720
Ser Leu Thr Leu Ile  *
```

```
TGCTGCTGCA GAGGAGGTCA CGCGTCCCCA AGGCCTCCTG TGACTGGCAG CATTGACTCT    780
GTGGCTTTGC CATCGTTTCC ATGACAACAG ACACAACACA GTTCTCGGGG CTCAGGAGGG    840
GAAGTCCAGC CTACCAGGCA CGTCTGCAGA AACAGTGCAA GGAAGGGCAG CGACTTCCTG    900
GTTGAGCTTC TGCTAAAACA TGGACATGCT TCAGTGCTGC TCCTGAGAGA GTAGCAGGTT    960
ACCACTCTGG CAGGCCCCAG CCCTGCAGCA AGGAGGAAGA GGACTCAAAA GTCTGGCCTT   1020
TCACTGAGCC CCCACAGCAG TGGGGGAGAA GCAAGGGTTG GGCCCAGTGT CCCCTTTCCC   1080
CAGTGACACC TCAGCCTTGG CAGCCCTGAT GACTGGTCTC TGGCTGCAAC TTAATGCTCT   1140
GATATGGCTT TTAGCATTTA TTATATGAAA ATAGCAGGGT TTTAGTTTTT AATTTATCAG   1200
AGACCCTGCC ACCCATTCCA TCTCCATCCA AGCAAACTGA ATGGCATTGA AACAAACTGG   1260
AGAAGAAGGT AGGAGAAAGG GCGGTGAACT CTGGCTCTTT GCTGTGGACA TGCGTGACCA   1320
GCAGTACTCA GGTTTGAGGG TTTGCAGAAA GCCAGGGAAC CCACAGAGTC ACCAACCCTT   1380
CATTTAACAA GTAAGAATGT TAAAAAGTGA AAACAATGTA AGAGCCTAAC TCCATCCCCC   1440
GTGGCCATTA CTGCATAAAA TAGAGTGCAT CCCGCCCGAA TTC                     1483
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 230 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Asp Gly His Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile
 1               5                  10                  15
Cys Gln Thr His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala
            20                  25                  30
Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp
        35                  40                  45
Pro Tyr Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys
    50                  55                  60
Glu Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala
65                  70                  75                  80
Ser Arg Pro Val Ile Gly Thr Asn Ala Val Ser Ile Glu Thr Asn Ile
                85                  90                  95
Pro Leu Gln Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr
            100                 105                 110
Leu Gly Asp Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys
        115                 120                 125
Cys Ala Asp Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser
    130                 135                 140
Val Phe Gly Val His Glu Cys Ala Met Gln Cys His Gly Arg Gly Val
145                 150                 155                 160
Cys Asn Asn Arg Lys Asn Cys His Cys Glu Ala His Trp Ala Pro Pro
                165                 170                 175
Phe Cys Asp Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile
            180                 185                 190
Arg Gln Ala Glu Ala Arg Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg
        195                 200                 205
Gly Gln Gly Gln Glu Pro Val Gly Ser Gln Glu His Ala Ser Thr Ala
    210                 215                 220
Ser Leu Thr Leu Ile  *
225                 230
```

SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1569 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE:JM109 (pMel α-26N)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
GGG GAC CTC TGG ATC CCA GTG AAG AGC TTC GAC TCC AAG AAT CAT CCA      48
Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His Pro

GAA GTG CTG AAT ATT CGA CTA CAA CGG GAA AGC AAA GAA CTG ATC ATA      96
Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile Ile

AAT CTG GAA AGA AAT GAA GGT CTC ATT GCC AGC AGT TTC ACG GAA ACC     144
Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser Ser Phe Thr Glu Thr

CAC TAT CTG CAA GAC GGT ACT GAT GTC TCC CTC GCT CGA AAT TAC ACG     192
His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr Thr

GGT CAC TGT TAC TAC CAT GGA CAT GTA CGG GGA TAT TCT GAT TCA GCA     240
Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser Ala

GTC AGT CTC AGC ACG TGT TCT GGT CTC AGG GGA CTT ATT GGG TTT GAA     288
Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Gly Phe Glu

AAT GAA AGC TAT GTC TTA GAA CCA ATG AAA AGT GCA ACC AAC AGA TAC     336
Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg Tyr

AAA CTC TTC CCA GCG AAG AAG CTG AAA AGC GTC CGG GGA TCA TGT GGA     384
Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg Gly Ser Cys Gly

TCA CAT CAC AAC ACA CCA AAC CTC GCT GCA AAG AAT GTG TTT CCA CCA     432
Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro Pro

CCC TCT CAG ACA TGG GCA AGA AGG CAT AAA AGA GAG ACC CTC AAG GCA     480
Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys Ala

ACT AAG TAT GTG GAG CTG GTG ATC GTG GCA GAC AAC CGA GAG TTT CAG     528
Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln

AGG CAA GGA AAA GAT CTG GAA AAA GTT AAG CAG CGA TTA ATA GAG ATT     576
Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile

GCT AAT CAC GTT GAC AAG TTT TAC AGA CCA CTG AAC ATT CGG ATC GTG     624
Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val

TTG GTA GGC GTG GAA GTG TGG AAT GAC ATG GAC AAA TGC TCT GTA AGT     672
Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val Ser
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```
CAG GAC CCA TTC ACC AGC CTC CAT GAA TTT CTG GAC TGG AGG AAG ATG      720
Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys Met

AAG CTT CTA CCT CGC AAA TCC CAT GAC AAT GCG CAG CTT GTC AGT GGG      768
Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser Gly

GTT TAT TTC CAA GGG ACC ACC ATC GGC ATG GCC CCA ATC ATG AGC ATG      816
Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met

TGC ACG GCA GAC CAG TCT GGG GGA ATT GTC ATG GAC CAT TCA GAC AAT      864
Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp Asn

CCC CTT GGT GCA GCC GTG ACC CTG GCA CAT GAG CTG GGC CAC AAT TTC      912
Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe

GGG ATG AAT CAT GAC ACA CTG GAC AGG GGC TGT AGC TGT CAA ATG GCG      960
Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met Ala

GTT GAG AAA GGA GGC TGC ATC ATG AAC GCT TCC ACC GGG TAC CCA TTT     1008
Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro Phe

CCC ATG GTG TTC AGC AGT TGC AGC AGG AAG GAC TTG GAG ACC AGC CTG     1056
Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser Leu

GAG AAA GGA ATG GGG GTG TGC CTG TTT AAC CTG CCG GAA GTC AGG GAG     1104
Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg Glu

TCT TTC GGG GGC CAG AAG TGT GGG AAC AGA TTT GTG GAA GAA GGA GAG     1152
Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly Glu

GAG TGT GAC TGT GGG GAG CCA GAG GAA TGT ATG AAT CGC TGC TGC AAT     1200
Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys Asn

GCC ACC ACC TGT ACC CTG AAG CCG GAC GCT GTG TGC GCA CAT GGG CTG     1248
Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly Leu

TGC TGT GAA GAC TGC CAG CTG AAG CCT GCA GGA ACA GCG TGC AGG GAC     1296
Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg Asp

TCC AGC AAC TCC TGT GAC CTC CCA GAG TTC TGC ACA GGG GCC AGC CCT     1344
Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser Pro

CAC TGC CCA GCC AAC GTG TAC CTG CAC GAT GGG CAC TCA TGT CAG GAT     1392
His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln Asp

GTG GAC GGC TAC TGC TAC AAT GGC ATC TGC CAG ACT CAC GAG CAG CAG     1440
Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln Gln

TGT GTC ACG CTC TGG GGA CCA GGT GCT AAA CCT GCC CCT GGG ATC TGC     1488
Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile Cys

TTT GAG AGA GTC AAT TCT GCA GGT GAT CCT TAT GGC AAC TGT GGC AAA     1536
Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly Lys
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```
GTC TCG AAG AGT TCC TTT GCC AAA TGC GAG ATG                    1569
Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met
```

SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 523 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His Pro

Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile Ile

Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser Ser Phe Thr Glu Thr

His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr Thr

Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser Ala

Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Gly Phe Glu

Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg Tyr

Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg Gly Ser Cys Gly

Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro Pro

Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys Ala

-1 1

Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln

Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile

Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val

Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val Ser

Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys Met

Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser Gly

Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met

Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp Asn

Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe

Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met Ala

Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro Phe

Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser Leu
Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg Glu
Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly Glu
Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys Asn
Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly Leu
Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg Asp
Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser Pro
His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln Asp
Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln Gln
Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile Cys
Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly Lys
Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met

SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2404 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE:JM109 (pMel β-24C)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
TGC TGC CAC CAG TGT AAG CTG TTG GCT CCT GGG ACC CTG TGC CGC GAG      48
Cys Cys His Gln Cys Lys Leu Leu Ala Pro Gly Thr Leu Cys Arg Glu

CAG GCC AGG CAG TGT GAC CTC CCG GAG TTC TGT ACG GGC AAG TCT CCC      96
Gln Ala Arg Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys Ser Pro

CAC TGC CCT ACC AAC TTC TAC CAG ATG GAT GGT ACC CCC TGT GAG GGC     144
His Cys Pro Thr Asn Phe Tyr Gln Met Asp Gly Thr Pro Cys Glu Gly

GGC CAG GCC TAC TGC TAC AAC GGC ATG TGC CTC ACC TAC CAG GAG CAG     192
Gly Gln Ala Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln Glu Gln

TGC CAG CAG CTG TGG GGA CCC GGA GCC CGA CCT GCC CCT GAC CTC TGC     240
Cys Gln Gln Leu Trp Gly Pro Gly Ala Arg Pro Ala Pro Asp Leu Cys

TTC GAG AAG GTG AAT GTG GCA GGA GAC ACC TTT GGA AAC TGT GGA AAG     288
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Phe Glu Lys Val Asn Val Ala Gly Asp Thr Phe Gly Asn Cys Gly Lys

GAC ATG AAT GGT GAA CAC AGG AAG TGC AAC ATG AGA GAT GCG AAG TGT      336
Asp Met Asn Gly Glu His Arg Lys Cys Asn Met Arg Asp Ala Lys Cys

GGG AAG ATC CAG TGT CAG AGC TCT GAG GCC CGG CCC CTG GAG TCC AAC      384
Gly Lys Ile Gln Cys Gln Ser Ser Glu Ala Arg Pro Leu Glu Ser Asn

GCG GTG CCC ATT GAC ACC ACT ATC ATC ATG AAT GGG AGG CAG ATC CAG      432
Ala Val Pro Ile Asp Thr Thr Ile Ile Met Asn Gly Arg Gln Ile Gln

TGC CGG GGC ACC CAC GTC TAC CGA GGT CCT GAG GAG GAG GGT GAC ATG      480
Cys Arg Gly Thr His Val Tyr Arg Gly Pro Glu Glu Glu Gly Asp Met

CTG GAC CCA GGG CTG GTG ATG ACT GGA ACC AAG TGT GGC TAC AAC CAT      528
Leu Asp Pro Gly Leu Val Met Thr Gly Thr Lys Cys Gly Tyr Asn His

ATT TGC CTT GAG GGG CAG TGC AGG AAC ACC TCC TTC TTT GAA ACT GAA      576
Ile Cys Leu Glu Gly Gln Cys Arg Asn Thr Ser Phe Phe Glu Thr Glu

GGC TGT GGG AAG AAG TGC AAT GGC CAT GGG GTC TGT AAC AAC AAC CAG      624
Gly Cys Gly Lys Lys Cys Asn Gly His Gly Val Cys Asn Asn Asn Gln

AAC TGC CAC TGC CTG CCG GGC TGG GCC CCG CCC TTC TGC AAC ACA CCG      672
Asn Cys His Cys Leu Pro Gly Trp Ala Pro Pro Phe Cys Asn Thr Pro

GGC CAC GGG GGC AGT ATC GAC AGT GGG CCT ATG CCC CCT GAG AGT GTG      720
Gly His Gly Gly Ser Ile Asp Ser Gly Pro Met Pro Pro Glu Ser Val

GGT CCT GTG GTA GCT GGA GTG TTG GTG GCC ATC TTG GTG CTG GCG GTC      768
Gly Pro Val Val Ala Gly Val Leu Val Ala Ile Leu Val Leu Ala Val

CTC ATG CTG ATG TAC TAC TGC TGC AGA CAG AAC AAC AAA CTA GGC CAA      816
Leu Met Leu Met Tyr Tyr Cys Cys Arg Gln Asn Asn Lys Leu Gly Gln

CTC AAG CCC TCA GCT CTC CCT TCC AAG CTG AGG CAA CAG TTC AGT TGT      864
Leu Lys Pro Ser Ala Leu Pro Ser Lys Leu Arg Gln Gln Phe Ser Cys

CCC TTC AGG GTT TCT CAG AAC AGC GGG ACT GGT CAT GCC AAC CCA ACT      912
Pro Phe Arg Val Ser Gln Asn Ser Gly Thr Gly His Ala Asn Pro Thr

TTC AAG CCG GAA TTC CGG GCC CCC CAC AGC CCA CAC CAC CAT GAC AAG      960
Phe Lys Pro Glu Phe Arg Ala Pro His Ser Pro His His His Asp Lys

GGC CAC CAA TTC CAC GGC CAC ACC CTC CTC CAC TCT GGG GAC GAC CCG     1008
Gly His Gln Phe His Gly His Thr Leu Leu His Ser Gly Asp Asp Pro

GAT CCT CAC TGA GCTGACCACA ACAGCCACTA CAACTGCAGC CACTGGATCC         1060
Asp Pro His  *

ACGGCCACCC TGTCCTCCAC CCCAGGGACC ACCTGGATCC TCACAGAGCC GAGCACTATA  1120
GCCACCGTGA TGGTGCCCAC CGGTTCCACG GCCACCGCCT CCTCCACTCT GGGAACAGCT  1180
CACACCCCCA AAGTGGTGAC CACCATGGCC ACTATGCCCA CAGCCACTGC CTCCACGGTT  1240
CCCAGCTCGT CCACCGTGGG GACCACCCGC ACCCCTGCAG TGCTCCCCAG CAGCCTGCCA  1300
ACCTTCAGCG TGTCCACTGT GTCCTCCTCA GTCCTCACCA CCCTGAGACC CACTGGCTTC  1360
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CCCAGCTCCC ACTTCTCTAC TCCCTGCTTC TGCAGGGCAT TTGGACAGTT TTTCTCGCCC   1420
GGGGAAGTCA TCTACAATAA GACCGACCGA GCCGGCTGCC ATTTCTACGC AGTGTGCAAT   1480
CAGCACTGTG ACATTGACCG CTTCCAGGGC GCCTGTCCCA CCTCCCCACC GCCAGTGTCC   1540
TCCGCCCCGC TGTCCTCGCC CTCCCCTGCC CCTGGCTGTG ACAATGCCAT CCCTCTCCGG   1600
CAGGTGAATG AGACCTGGAC CCTGGAGAAC TGCACGGTGG CCAGGTGCGT GGGTGACAAC   1660
CGTGTCGTCC TGCTGGACCC AAAGCCTGTG GCCAACGTCA CCTGCGTGAA CAAGCACCTG   1720
CCCATCAAAG TGTCGGACCC GAGCCAGCCC TGTGACTTCC ACTATGAGTG CGAGTGCATC   1780
TGCAGCATGT GGGGCGGCTC CCACTATTCC ACCTTTGACG GCACCTCTTA CACCTTCCGG   1840
GGCAACTGCA CCTATGTCCT CATGAGAGAG ATCCATGCAC GCTTTGGGAA TCTCAGCCTC   1900
TACCTGGACA ACCACTACTG CACGGCCTCT GCCACTGCCG CTGCCGCCCG CTGCCCCCGC   1960
GCCCTCAGCA TCCACTACAA GTCCATGGAT ATCGTCCTCA CTGTCACCAT GGTGCATGGG   2020
AAGGAGGAGG GCCTGATCCT GTTTGACCAA ATTCCGGTGA GCAGCGGTTT CAGCAAGAAC   2080
GGCGTGCTTG TGTCTGTGCT GGGGACCACC ACCATGCGTG TGGACATTCC TGCCCTGGGC   2140
GTGAGCGTCA CCTTCAATGG CCAAGTCTTC CAGGCCCGGC TGCCCTACAG CCTCTTCCAC   2200
AACAACACCG AGGGCCAGTG CGGCACCTGC ACCAACAACC AGAGGGACGA CTGTCTCCAG   2260
CGGGACGGAA CCACTGCCGC CAGTTGCAAG GACATGGCCA AGACGTGGCT GGTCCCCGAC   2320
AGCAGAAAGG ATGGCTGCTG GGCCCCGACT GGCACACCCC CCACTGCCAG CCCCGCAGCC   2380
CCGGTGTCTA GCACACCCAC CCCG                                          2404
```

SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 339 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Cys Cys His Gln Cys Lys Leu Leu Ala Pro Gly Thr Leu Cys Arg Glu
 1               5                  10                  15
Gln Ala Arg Gln Cys Asp Leu Pro Glu Phe Cys Thr Gly Lys Ser Pro
            20                  25                  30
His Cys Pro Thr Asn Phe Tyr Gln Met Asp Gly Thr Pro Cys Glu Gly
        35                  40                  45
Gly Gln Ala Tyr Cys Tyr Asn Gly Met Cys Leu Thr Tyr Gln Glu Gln
    50                  55                  60
Cys Gln Gln Leu Trp Gly Pro Gly Ala Arg Pro Ala Pro Asp Leu Cys
65                  70                  75                  80
Phe Glu Lys Val Asn Val Ala Gly Asp Thr Phe Gly Asn Cys Gly Lys
                85                  90                  95
Asp Met Asn Gly Glu His Arg Lys Cys Asn Met Arg Asp Ala Lys Cys
            100                 105                 110
Gly Lys Ile Gln Cys Gln Ser Ser Glu Ala Arg Pro Leu Glu Ser Asn
        115                 120                 125
Ala Val Pro Ile Asp Thr Thr Ile Ile Met Asn Gly Arg Gln Ile Gln
    130                 135                 140
Cys Arg Gly Thr His Val Tyr Arg Gly Pro Glu Glu Glu Gly Asp Met
145                 150                 155                 160
Leu Asp Pro Gly Leu Val Met Thr Gly Thr Lys Cys Gly Tyr Asn His
                165                 170                 175
Ile Cys Leu Glu Gly Gln Cys Arg Asn Thr Ser Phe Phe Glu Thr Glu
            180                 185                 190
Gly Cys Gly Lys Lys Cys Asn Gly His Gly Val Cys Asn Asn Asn Gln
        195                 200                 205

Asn Cys His Cys Leu Pro Gly Trp Ala Pro Pro Phe Cys Asn Thr Pro
    210                 215                 220
Gly His Gly Gly Ser Ile Asp Ser Gly Pro Met Pro Pro Glu Ser Val
225                 230                 235                 240
Gly Pro Val Val Ala Gly Val Leu Val Ala Ile Leu Val Leu Ala Val
                245                 250                 255
Leu Met Leu Met Tyr Tyr Cys Cys Arg Gln Asn Asn Lys Leu Gly Gln
            260                 265                 270
Leu Lys Pro Ser Ala Leu Pro Ser Lys Leu Arg Gln Gln Phe Ser Cys
        275                 280                 285
Pro Phe Arg Val Ser Gln Asn Ser Gly Thr Gly His Ala Asn Pro Thr
    290                 295                 300
Phe Lys Pro Glu Phe Arg Ala Pro His Ser Pro His His His Asp Lys
305                 310                 315                 320
Gly His Gln Phe His Gly His Thr Leu Leu His Ser Gly Asp Asp Pro
                325                 330                 335
Asp Pro His
        339
```

SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 453 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(vii) IMMEDIATE SOURCE

(B) CLONE :JM109 (pMel β-24N)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
C GGA GCT GCC ACT GGG CAC CCC TTT CCC AAA GTG TTC AAT GGA TGC          46
  Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys

AAC AGG AGG GAG CTG GAC AGG TAT CTG CAG TCA GGT GGT GGA ATG TGT        94
Asn Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys

CTC TCC AAC ATG CCA GAC ACC AGG ATG TTG TAT GGA GGC CGG AGG TGT       142
Leu Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys

GGG AAC GGG TAT CTG GAA GAT GGG GAA GAG TGT GAC TGT GGA GAA GAA       190
Gly Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu

GAG GAA TGT AAC AAC CCC TGC TGC AAT GCC TCT AAT TGT ACC CTG AGG       238
Glu Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg

CCG GGG GCG GAG TGT GCT CAC GGC TCC TGC TGC CAC CAG TGT AAG CTG       286
Pro Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu

TTG GCT CCT GGG ACC CTG TGC CGC GAG CAG GCC AGG CAG TGT GAC CTC       334
Leu Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu

CCG GAG TTC TGT ACG GGC AAG TCT CCC CAC TGC CCT ACC AAC TTC TAC       382
Pro Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr

CAG ATG GAT GGT ACC CCC TGT GAG GGC GGC CAG GCC TAC TGC TAC AAC       430
Gln Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn

GGC ATG TGC CTC ACC TAC CAG GA                                        453
Gly Met Cys Leu Thr Tyr Gln
```

INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 150 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Gly Ala Ala Thr Gly His Pro Phe Pro Lys Val Phe Asn Gly Cys Asn
 1               5                  10                  15
Arg Arg Glu Leu Asp Arg Tyr Leu Gln Ser Gly Gly Gly Met Cys Leu
            20                  25                  30
Ser Asn Met Pro Asp Thr Arg Met Leu Tyr Gly Gly Arg Arg Cys Gly
        35                  40                  45
Asn Gly Tyr Leu Glu Asp Gly Glu Glu Cys Asp Cys Gly Glu Glu Glu
    50                  55                  60
Glu Cys Asn Asn Pro Cys Cys Asn Ala Ser Asn Cys Thr Leu Arg Pro
65                  70                  75                  80
Gly Ala Glu Cys Ala His Gly Ser Cys Cys His Gln Cys Lys Leu Leu
                85                  90                  95
Ala Pro Gly Thr Leu Cys Arg Glu Gln Ala Arg Gln Cys Asp Leu Pro
            100                 105                 110
Glu Phe Cys Thr Gly Lys Ser Pro His Cys Pro Thr Asn Phe Tyr Gln
        115                 120                 125
Met Asp Gly Thr Pro Cys Glu Gly Gly Gln Ala Tyr Cys Tyr Asn Gly
    130                 135                 140
Met Cys Leu Thr Tyr Gln
145                 150
```

Claims

1. A soluble meltrin polypeptide which does not comprise a transmembrane domain or an intracellular domain and which comprises the amino acid sequence of Glu (No. 156) to Ile (No. 686) from the N-terminal in Fig. 15a - Fig. 15f.

2. A polypeptide of claim 1 which comprises the amino acid sequence of Gly (No. 1) to Ile (No. 686) from the N-terminal in Fig. 15a - Fig. 15f.

3. A DNA comprising a base sequence encoding a polypeptide of claim 1 or 2.

4. A DNA of claim 3 which comprises the base sequence of No. 1 to No. 2058 from the 5' terminal in Fig. 15a - Fig. 15f.

5. A DNA of claim 3 which comprises the base sequence of No. 1 to No. 2848 from the 5' terminal in Fig. 15a - Fig. 15f.

6. An antisense oligonucleotide which hybridizes with a part of the sequence of No. 1957 to No. 2848 from the 5' terminal in Fig. 15a - Fig. 15f.

7. An antisense oligonucleotide of claim 6 which inhibits the expression of the polypeptide of claim 1 or 2.

8. An antibody which recognizes the C-terminal region of a soluble meltrin wherein the C-terminal region is from amino acid No. 653 to No. 686 from the amino terminal in Fig. 15a - Fig. 15f.

9. An antibody of claim 8 which is a polyclonal antibody obtained from a mouse.

10. 4. An antibody of claim 8 which is a monoclonal antibody.

11. An antibody of claim 10 which is a monoclonal antibody obtained from a hybridoma using mouse spleen cells and lymphocytes.

12. A method for the preparation of an antibody which method comprises:

    - immunizing an animal with a polypeptide of claim 1 or 2; and
    - obtaining an antibody from the immunized animal.

13. A vector comprising a DNA of any one of claims 3 to 5.

14. A transformant by the vector of claim 13.

15. A process for producing a polypeptide of claim 1 or 2, which process comprises culturing the appropriate transformant of claim 14.

16. A medical composition comprising a polypeptide of claim 1 or 2, an antisense oligonucleotide of claim 6 or 7 or an antibody of any one of claims 8 to 11.

17. Use of a polypeptide of claim 1 or 2, an antisense oligonucleotide of claim 6 or 7 or an antibody of any one of claims 8 to 11 for the manufacture of a medicament for treatment of a condition associated with unhealthy enhanced bone resorption.

18. Use according to claim 17, wherein the condition associated with unhealthy enhanced bone resorption is osteoporosis or hypercalsemia.

19. Use of a polypeptide of claim 1 or 2, an antisense oligonucleotide of claim 6 or 7 or an antibody of any one of claims 8 to 11 for the manufacture of a medicament for preventing metastasis of cancer cells.

Patentansprüche

1. Lösliches Meltrin-Polypeptid, nicht umfassend eine Transmembrandomäne oder eine intrazelluläre Domäne und umfassend die Aminosäuresequenz von Glu (Nr. 156) bis Ile (Nr. 686) von dem N-Terminus in Fig. 15a - Fig. 15f.

2. Polypeptid nach Anspruch 1, umfassend die Aminosäuresequenz von Gly (Nr. 1) bis Ile (Nr. 686) von dem N-Terminus in Fig. 15a - Fig. 15f.

3. DNA, umfassend eine Basensequenz, welche ein Polypeptid nach Anspruch 1 oder 2 kodiert.

4. DNA nach Anspruch 3, umfassend die Basensequenz von Nr. 1 bis Nr. 2058 von dem 5'-Terminus in Fig. 15a - Fig. 15f.

5. DNA nach Anspruch 3, umfassend die Basensequenz von Nr. 1 bis Nr. 2848 von dem 5'-Terminus in Fig. 15a - Fig. 15f.

6. Antisense-Oligonucleotid, welches mit einem Teil der Sequenz von Nr. 1957 bis Nr. 2848 von dem 5'-Terminus in Fig. 15a - Fig. 15f hybridisiert.

7. Antisense-Oligonucleotid nach Anspruch 6, welches die Expression des Polypeptids nach Anspruch 1 oder 2 inhibiert.

8. Antikörper, welcher die C-terminale Region eines löslichen Meltrins erkennt, wobei sich die C-terminale Region von Aminosäure Nr. 653 bis Nr. 686 von dem Aminoterminus in Fig. 15a - Fig. 15f erstreckt.

9. Antikörper nach Anspruch 8, welcher ein polyklonaler Antikörper ist, der von einer Maus erhalten wurde.

10. Antikörper nach Anspruch 8, welcher ein monoklonaler Antikörper ist.

11. Antikörper nach Anspruch 10, welcher ein monoklonaler Antikörper ist, erhalten aus einem Hybridom unter Verwendung von Mäusemilzzellen und Lymphozyten.

12. Verfahren zur Herstellung eines Antikörpers, wobei das Verfahren umfasst:

    - Immunisieren eines Tieres mit einem Polypeptid nach Anspruch 1 oder 2; und
    - Erhalten eines Antikörpers aus dem immunisierten Tier.

13. Vektor, umfassend eine DNA nach einem der Ansprüche 3 bis 5.

14. Transformant durch den Vektor nach Anspruch 13.

15. Verfahren zur Herstellung eines Polypeptids nach Anspruch 1 oder 2, wobei das Verfahren Kultivieren des geeigneten Transformanten nach Anspruch 14 umfasst.

16. Arzneimittel, umfassend ein Polypeptid nach Anspruch 1 oder 2, ein Antisense-Oligonucleotid nach Anspruch 6 oder 7 oder einen Antikörper nach einem der Ansprüche 8 bis 11.

17. Verwendung eines Polypeptids nach Anspruch 1 oder 2, eines Antisense-Oligonucleotids nach Anspruch 6 oder 7 oder eines Antikörpers nach einem der Ansprüche 8 bis 11 zur Herstellung eines Medikaments zur Behandlung eines Zustandes, der mit krankhafter gesteigerter Knochenresorption in Zusammenhang steht.

18. Verwendung gemäß Anspruch 17, wobei der Zustand, der mit krankhafter gesteigerter Knochenresorption in Zusammenhang steht, Osteoporose oder Hyperkalzämie ist.

19. Verwendung eines Polypeptids nach Anspruch 1 oder 2, eines Antisense-Oligonucleotids nach Anspruch 6 oder 7 oder eines Antikörpers nach einem der Ansprüche 8 bis 11 zur Herstellung eines Medikaments zur Verhinderung einer Metastasierung von Krebszellen.

Revendications

1. Polypeptide de meltrine soluble, qui ne comporte pas un domaine transmembranaire ou un domaine intracellulaire et qui comporte la séquence d'acides aminés allant du résidu Glu n° 156 au résidu Ile n° 686 du domaine N-terminal présenté sur les figures 15a à 15f.

2. Polypeptide conforme à la revendication 1, qui comporte la séquence d'acides aminés allant du résidu Gly n° 1 au résidu Ile n° 686 du domaine N-terminal présenté sur les figures 15a à 15 f.

3. ADN comportant une séquence de bases qui code un polypeptide conforme à la revendication 1 ou 2.

4. ADN conforme à la revendication 3, qui comporte la séquence de bases allant de la base n° 1 à la base n° 2058 du domaine 5'-terminal présenté sur les figures 15a à 15f.

5. ADN conforme à la revendication 3, qui comporte la séquence de bases allant de la base n° 1 à la base n° 2848 du domaine 5'-terminal présenté sur les figures 15a à 15f.

6. Oligonucléotide anti-sens qui s'hybride avec une partie de la séquence allant de la base n° 1957 à la base n° 2848 du domaine 5'-terminal présenté sur les figures 15a à 15f.

7. Oligonucléotide anti-sens conforme à la revendication 6, qui inhibe l'expression d'un polypeptide conforme à la revendication 1 ou 2.

8. Anticorps reconnaissant un domaine C-terminal d'une meltrine soluble, lequel domaine C-terminal va du résidu d'acide aminé n° 653 3 au résidu n° 686 du domaine amino-terminal présenté sur les figures 15a à 15f.

9. Anticorps conforme à la revendication 8, qui est un anticorps polyclonal obtenu chez une souris.

10. Anticorps conforme à la revendication 8, qui est un anticorps monoclonal.

11. Anticorps conforme à la revendication 10, qui est un anticorps monoclonal obtenu à partir d'un hybridome formé avec des cellules spléniques de souris et des lymphocytes.

12. Procédé de préparation d'un anticorps, lequel procédé comporte :

    - le fait d'immuniser un animal avec un polypeptide conforme à la revendication 1 ou 2,
    - et le fait de récupérer un anticorps chez cet animal immunisé.

13. Vecteur comprenant un ADN conforme à l'une des revendications 3 à 5.

14. Organisme transformé avec un vecteur conforme à la revendication 13.

15. Procédé de production d'un polypeptide conforme à la revendication 1 ou 2, lequel procédé comporte le fait de cultiver un organisme transformé approprié, conforme à la revendication 14.

16. Composition médicale comprenant un polypeptide conforme à la revendication 1 ou 2, un oligonucléotide anti-sens conforme à la revendication 6 ou 7, ou un anticorps conforme à l'une des revendications 8 à 11.

17. Emploi d'un polypeptide conforme à la revendication 1 ou 2, d'un oligonucléotide anti-sens conforme à la revendication 6 ou 7, ou d'un anticorps conforme à l'une des revendications 8 à 11, en vue de la fabrication d'un médicament conçu pour le traitement d'un état associé à une augmentation pathologique de la résorption osseuse.

18. Emploi conforme à la revendication 17, pour lequel l'état associé à une augmentation pathologique de la résorption osseuse est une ostéoporose ou une hypercalcémie.

19. Emploi d'un polypeptide conforme à la revendication 1 ou 2, d'un oligonucléotide anti-sens conforme à la revendication 6 ou 7, ou d'un anticorps conforme à l'une des revendications 8 à 11, en vue de la fabrication d'un médicament conçu pour prévenir la métastase de cellules cancéreuses.

FIG.1a

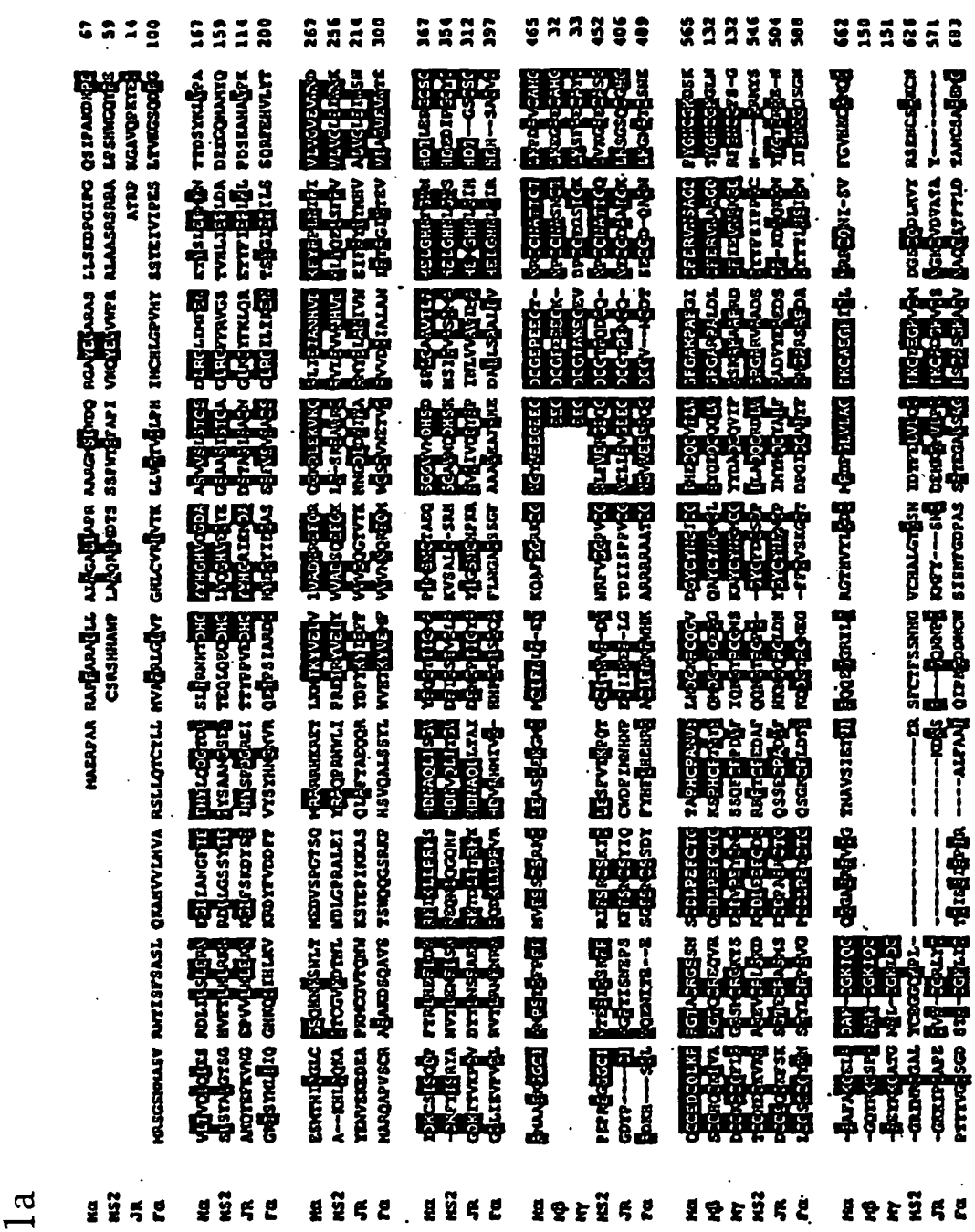

FIG.1b

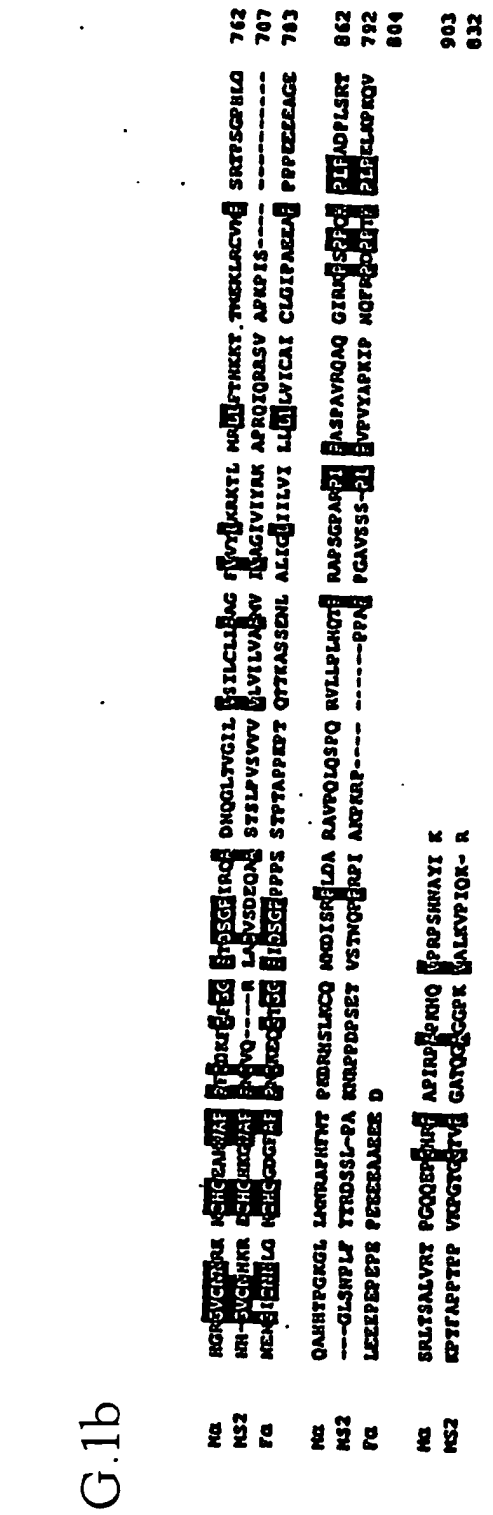

FIG.2a

```
        190        200        210        220        230        240
CGCGGGGCCCCCGAAGCAGCTGCACGCCAGGCCGGCGACAATGGCAGAGCGCCCGGCGCG
                                          M  A  E  R  P  A  R      7

        250        260        270        280        290        300
GCGCGCGCCCCCCGCCCGCGCCCTCCTGCTGGCCCTGGCTGGGGCCCTGCTGGCGCCCCG
 R  A  P  P  A  R  A  L  L  L  A  L  A  G  A  L  L  A  P  R     27

        310        320        330        340        350        360
TGCAGCCCGAGGGATGAGTTTGTGGGACCAGAGAGGAGCTTACGAAGTGGCCAGAGCCTC
 A  A  R  G  M  S  L  W  D  Q  R  G  A  Y  E  V  A  R  A  S     47

        370        380        390        400        410        420
CCTTCTGAGCAAGGACCCTGGGATCCCAGGACAGAGCATCCCAGCCAAGGATCATCCAGA
 L  L  S  K  D  P  G  I  P  G  Q  S  I  P  A  K  D  H  P  D     67

        430        440        450        460        470        480
CGTGCTGACTGTGCAACTGCAGCTGGAGAGCCGAGACCTGATCCTCAGCCTGGAAAGGAA
 V  L  T  V  Q  L  Q  L  E  S  R  D  L  I  L  S  L  E  R  N     87
```


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FIG.2b

```
        490        500        510        520        530        540
TGAGGGACTCATTGCCAATGGCTTCACGGAGACCCATTATCTGCAAGATGGTACTGATGT
 E  G  L  I  A  N  G  F  T  E  T  H  Y  L  Q  D  G  T  D  V     107

        550        560        570        580        590        600
CTCTCTCACTCGAAATCACACGGATCATTGTTACTACCATGGACATGTGCAAGGAGATGC
 S  L  T  R  N  H  T  D  H  C  Y  Y  H  G  H  V  Q  G  D  A     127

        610        620        630        640        650        660
TGCATCAGTGGTCAGCCTCAGTACTTGCTCTGATCTCCGGGGACTTATCATGTTTGAAAA
 A  S  V  V  S  L  S  T  C  S  D  L  R  G  L  I  M  F  E  N     147

        670        680        690        700        710        720
TAAAACGTACAGCTTAGAGCCAATGAAAAACACCACTGACAGCTACAAACTCGTCCCAGC
 K  T  Y  S  L  E  P  M  K  N  T  T  D  S  Y  K  L  V  P  A     167

        730        740        750        760        770        780
TGAGAGCATGACGAACATCCAAGGGCTGTGTGGGTCACAGCATAACAAGTCCAACCTCAC
 E  S  M  T  N  I  Q  G  L  C  G  S  Q  H  N  K  S  N  L  T     187
```


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FIG. 2c

```
      790        800        810        820        830        840
CATGGAAGATGTCTCCCCTGGAACCTCTCAAATGCGGGCAAGAAGGCATAAGAGAGAGAC
 M  E  D  V  S  P  G  T  S  Q  M  R  A  R  R  H  K  R  E  T     207

      850        860        870        880        890        900
CCTTAAGATGACCAAGTACGTAGAGCTGGTTATTGTGGCAGACAACAGAGAGTTTCAGAG
 L  K  M  T  K  Y  V  E  L  V  I  V  A  D  N  R  E  F  Q  R     227

      910        920        930        940        950        960
GCAAGGAAAAGACCTGGAGAAAGTTAAGCAGCGATTAATAGAGATCGCCAATCACGTTGA
 Q  G  K  D  L  E  K  V  K  Q  R  L  I  E  I  A  N  H  V  D     247

      970        980        990       1000       1010       1020
CAAGTTTTACAGACCACTGAACATCCGGATCGTGCTGGTAGGAGTGGAAGTGTGGAATGA
 K  F  Y  R  P  L  N  I  R  I  V  L  V  G  V  E  V  W  N  D     267

     1030       1040       1050       1060       1070       1080
CATCGACAAATGCTCTATAAGCCAGGACCCATTCACCAGGCTCCATGAGTTTCTAGACTG
 I  D  K  C  S  I  S  Q  D  P  F  T  R  L  H  E  F  L  D  W     287
```


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FIG.2d

```
      1090       1100       1110       1120       1130       1140
GAGAAAGATAAAGCTTCTACCTCGAAAATCCCACGACAATGCTCAGCTTATCAGTGGGGT
 R  K  I  K  L  L  P  R  K  S  H  D  N  A  Q  L  I  S  G  V     307

      1150       1160       1170       1180       1190       1200
TTATTTCCAAGGAACCACCATCGGCATGGCACCCATCATGAGCATGTGCACTGCAGAACA
 Y  F  Q  G  T  T  I  G  M  A  P  I  M  S  M  C  T  A  E  Q     327

      1210       1220       1230       1240       1250       1260
GTCTGGAGGAGTTGTCATGGACCATTCAGACAGCCCCCTTGGTGCCGCAGTGACCTTGGC
 S  G  G  V  V  M  D  H  S  D  S  P  L  G  A  A  V  T  L  A     347

      1270       1280       1290       1300       1310       1320
ACATGAGCTGGGCCACAACTTCGGGATGAACCATGACACACTGGAGAGGGGCTGCAGCTG
 H  E  L  G  H  N  F  G  M  N  H  D  T  L  E  R  G  C  S  C     367

      1330       1340       1350       1360       1370       1380
CAGAATGGCCGCAGAGAAAGGAGGCTGCATCATGAACCCGTCCACGGGGTTCCCATTCCC
 R  M  A  A  E  K  G  G  C  I  M  N  P  S  T  G  F  P  F  P     387
```


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FIG.2e

```
      1390       1400       1410       1420       1430       1440
CATGGTGTTCAGCAGCTGCAGCAGGAAGGACCTGGAGGCTAGCCTGGAGAAGGGCATGGG
 M  V  F  S  S  C  S  R  K  D  L  E  A  S  L  E  K  G  M  G     407

      1450       1460       1470       1480       1490       1500
GATGTGCCTCTTCAACCTACCAGAGGTCAAGCAGGCCTTTGGGGGCCGGAAGTGTGGAAA
 M  C  L  F  N  L  P  E  V  K  Q  A  F  G  G  R  K  C  G  N     427

      1510       1520       1530       1540       1550       1560
TGGCTATGTGGAAGAGGGAGAAGAGTGTGACTGCGGAGAACCGGAGGAATGCACGAATCG
 G  Y  V  E  E  G  E  E  C  D  C  G  E  P  E  E  C  T  N  R     447

      1570       1580       1590       1600       1610       1620
CTGCTGTAACGCTACCACCTGTACTCTGAAGCCAGATGCTGTGTGCGCGCACGGGCAGTG
 C  C  N  A  T  T  C  T  L  K  P  D  A  V  C  A  H  G  Q  C     467

      1630       1640       1650       1660       1670       1680
CTGTGAAGACTGTCAGCTGAAGCCTCCAGGAACTGCATGCAGGGGCTCCAGCAACTCCTG
 C  E  D  C  Q  L  K  P  P  G  T  A  C  R  G  S  S  N  S  C     487
```


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FIG.2f

```
      1690       1700       1710       1720       1730       1740
TGACCTCCCAGAATTCTGCACAGGGACTGCCCCTCACTGTCCAGCCAATGTGTACCTACA
 D  L  P  E  F  C  T  G  T  A  P  H  C  P  A  N  V  Y  L  H     507

      1750       1760       1770       1780       1790       1800
TGATGGCCACCCGTGTCAGGGCGTGGATGGTTACTGCTACAACGGCATCTGCCAGACCCA
 D  G  H  P  C  Q  G  V  D  G  Y  C  Y  N  G  I  C  Q  T  H     527

      1810       1820       1830       1840       1850       1860
TGAGCAGCAGTGTGTCACGCTCTGGGGACCAGGTGCTAAACCGGCTCCTGGCATCTGCTT
 E  Q  Q  C  V  T  L  W  G  P  G  A  K  P  A  P  G  I  C  F     547

      1870       1880       1890       1900       1910       1920
TGAGCGAGTCAACTCTGCAGGAGATCCTTATGGTAACTGTGGCAAAGACTCCAAGAGCGC
 E  R  V  N  S  A  G  D  P  Y  G  N  C  G  K  D  S  K  S  A     567

      1930       1940       1950       1960       1970       1980
CTTCGCCAAATGTGAGCTGAGAGATGCCAAGTGTGGGAAAATCCAGTGTCAAGGTGGTGC
 F  A  K  C  E  L  R  D  A  K  C  G  K  I  Q  C  Q  G  G  A     587
```


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FIG. 2g

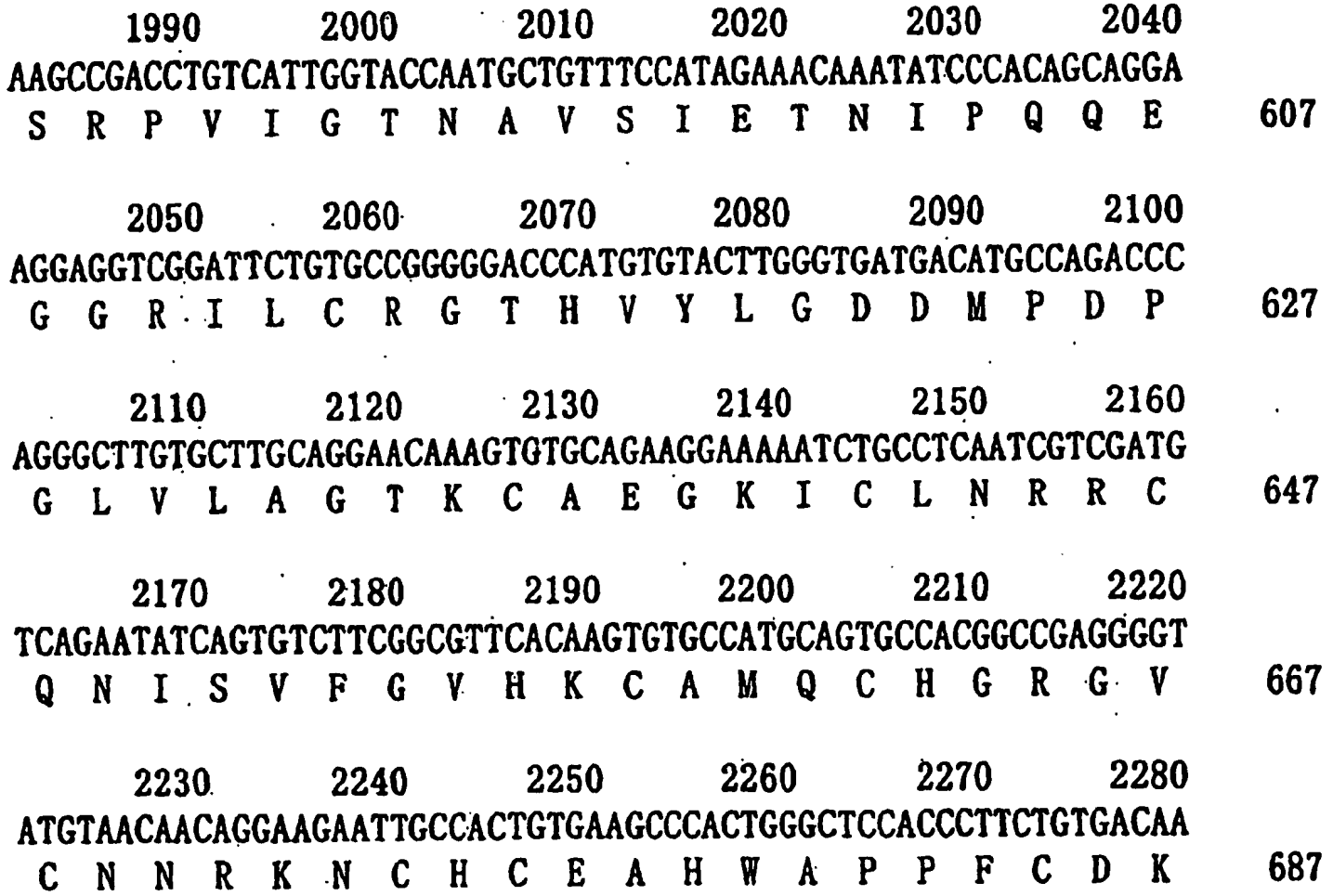

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FIG. 2h

```
      2290       2300       2310       2320       2330       2340
GTTTGGCTTTGGAGGAAGCACAGACAGTGGTCCCATCAGGCAAGCAGATAACCAGGGCTT
 F  G  F  G  G  S  T  D  S  G  P  I  R  Q  A  D  N  Q  G  L     707

      2350       2360       2370       2380       2390       2400
GACTGTAGGAATCCTGGTGAGCATCCTGTGTCTGCTTGCTGCTGGATTTGTGGTGTATCT
 T  V  G  I  L  V  S  I  L  C  L  L  A  A  G  F  V  V  Y  L     727

      2410       2420       2430       2440       2450       2460
CAAAAGGAAGACGTTGATGCGGCTGCTGTTCACACATAAAAAAACCACCATGGAAAAGCT
 K  R  K  T  L  M  R  L  L  F  T  H  K  K  T  T  M  E  K  L     747

      2470       2480       2490       2500       2510       2520
AAGGTGTGTGCACCCTTCCCGGACACCCAGTGGCCCTCACCTTGGCCAGGCTCACCACAC
 R  C  V  H  P  S  R  T  P  S  G  P  H  L  G  Q  A  H  H  T     767

      2530       2540       2550       2560       2570       2580
CCCCGGGAAAGGCCTGCTGATGAACCGGGCACCACATTTCAATACCCCCAAGGACAGGCA
 P  G  K  G  L  L  M  N  R  A  P  H  F  N  T  P  K  D  R  H     787
```


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FIG. 2i

```
      2590       2600       2610       2620       2630       2640
CTCGCTGAAATGCCAGAACATGGACATCAGCAGGCCCCTCGACGCTCGAGCCGTCCCACA
 S  L  K  C  Q  N  M  D  I  S  R  P  L  D  A  R  A  V  P  Q     807

      2650       2660       2670       2680       2690       2700
GCTTCAGTCACCTCAGCGAGTGCTCCTGCCTCTCCACCAGACCCCACGTGCACCCAGTGG
 L  Q  S  P  Q  R  V  L  L  P  L  H  Q  T  P  R  A  P  S  G     827

      2710       2720       2730       2740       2750       2760
CCCTGCCAGGCCCCTGCCCGCCAGTCCTGCAGTCAGGCAGGCCCAGGGCATTCGAAAACC
 P  A  R  P  L  P  A  S  P  A  V  R  Q  A  Q  G  I  R  K  P     847

      2770       2780       2790       2800       2810       2820
CAGTCCTCCTCAGAAGCCTCTGCCTGCTGATCCACTGAGCAGGACTTCTCGGCTCACTAG
 S  P  P  Q  K  P  L  P  A  D  P  L  S  R  T  S  R  L  T  S     867

      2830       2840       2850       2860       2870       2880
TGCCTTGGTGAGGACCCCAGGGCAGCAGGAACCTGGGCACCGCCCAGCCCCCATCAGACC
 A  L  V  R  T  P  G  Q  Q  E  P  G  H  R  P  A  P  I  R  P     887
```


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FIG. 2j

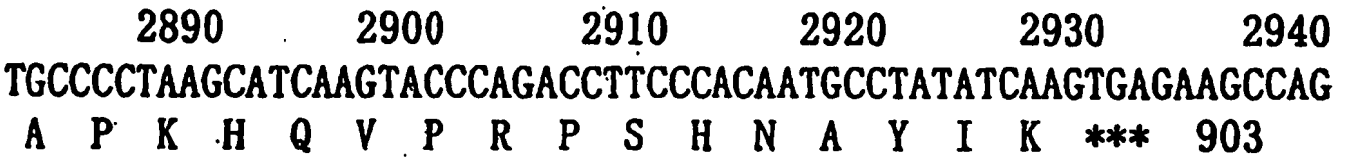
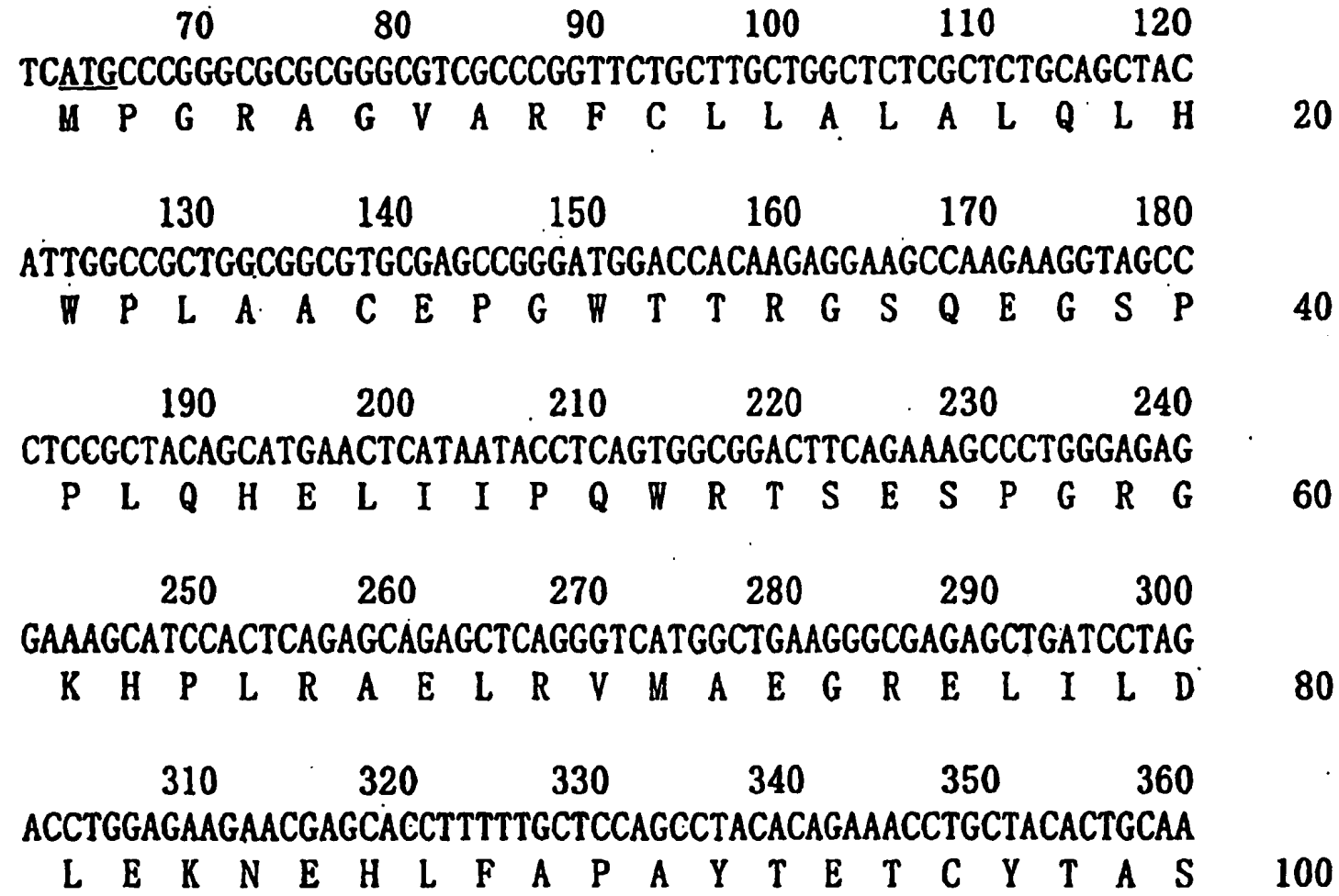

2890
2900
2910
2920
2930
2940
TGCCCCTAAGCATCAAGTACCCAGACCTTCCCACAATGCCTATATCAAGTGAGAAGCCAG
A P K H Q V P R P S H N A Y I K *** 903

FIG. 3a



101

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FIG. 3b

```
          370        380        390        400        410        420
GTGGCAATCCTCAAACCAGCACGCTGAAGTCTGAGGATCACTGCTTTTACCACGGGACTG
  G  N  P  Q  T  S  T  L  K  S  E  D  H  C  F  Y  H  G  T  V    120

          430        440        450        460        470        480
TGAGGGACGTGGATGAGTCCAGTGTCACGCTCAGCACCTGCCGGGGAATTAGAGGACTGA
  R  D  V  D  E  S  S  V  T  L  S  T  C  R  G  I  R  G  L  I    140

          490        500        510        520        530        540
TTATAGTGAGAAGTAACCTCAGCTACATCATCGAGCCCGTCCCTAACAGCGACAGCCAAC
  I  V  R  S  N  L  S  Y  I  I  E  P  V  P  N  S  D  S  Q  H    160

          550        560        570        580        590        600
ACCGTATTTACAGATCCGAACATCTCACGCTGCCCCCGGGGAACTGTGGGTTCGAGCACT
  R  I  Y  R  S  E  H  L  T  L  P  P  G  N  C  G  F  E  H  S    180

          610        620        630        640        650        660
CCGGGCCCACCTCGAAGGACTGGGCCCTTCAGTTTACACATCAGACCAAAAAGCAACCTC
  G  P  T  S  K  D  W  A  L  Q  F  T  H  Q  T  K  K  Q  P  R    200
```

FIG. 3c

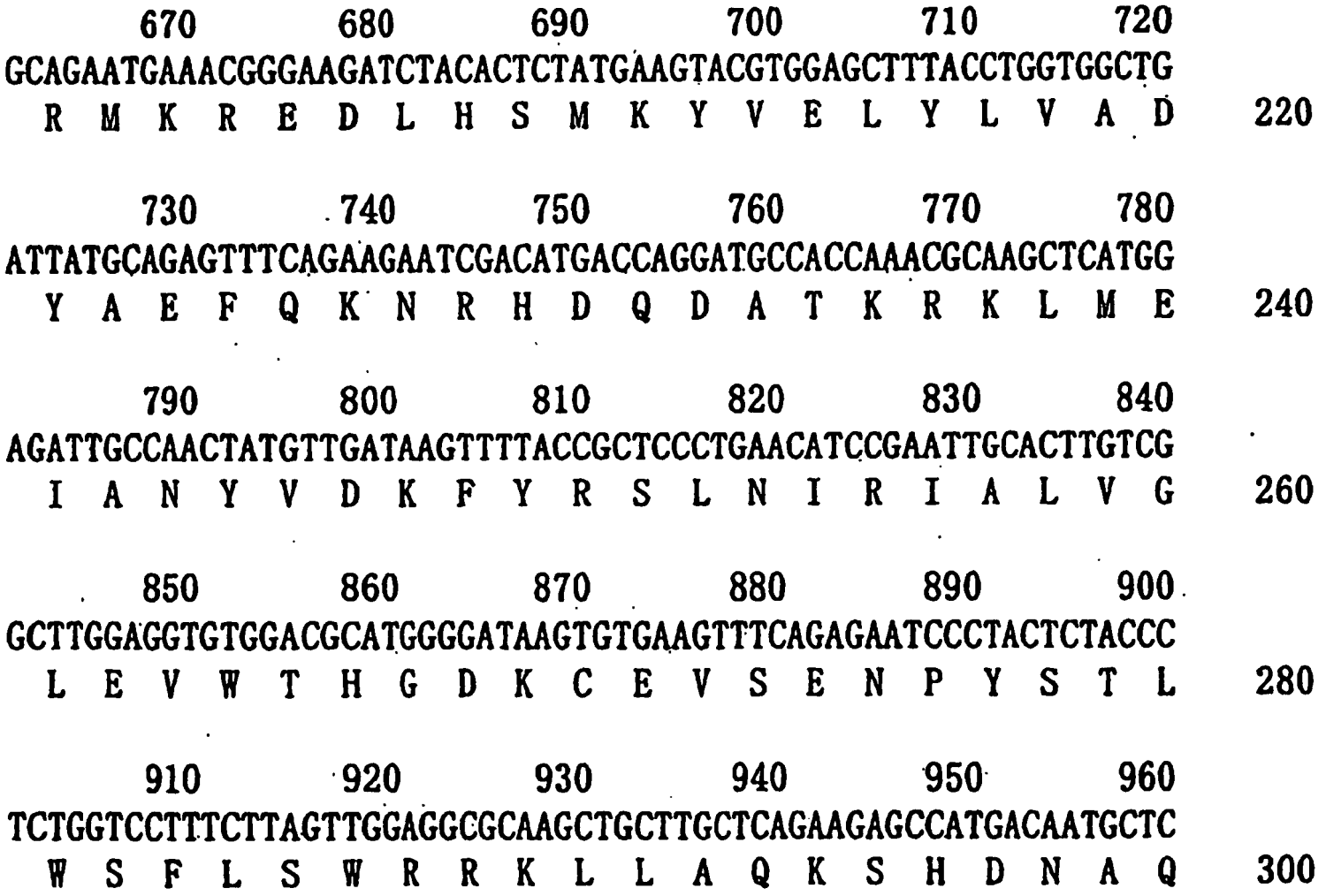
670 680 690 700 710 720
GCAGAATGAAACGGGAAGATCTACACTCTATGAAGTACGTGGAGCTTTACCTGGTGGCTG
R M K R E D L H S M K Y V E L Y L V A D 220
730 740 750 760 770 780
ATTATGCAGAGTTTCAGAAGAATCGACATGACCAGGATGCCACCAAACGCAAGCTCATGG
Y A E F Q K N R H D Q D A T K R K L M E 240
790 800 810 820 830 840
AGATTGCCAACTATGTTGATAAGTTTTACCGCTCCCTGAACATCCGAATTGCACTTGTCG
I A N Y V D K F Y R S L N I R I A L V G 260
850 860 870 880 890 900
GCTTGGAGGTGTGGACGCATGGGGATAAGTGTGAAGTTTCAGAGAATCCCTACTCTACCC
L E V W T H G D K C E V S E N P Y S T L 280
910 920 930 940 950 960
TCTGGTCCTTTCTTAGTTGGAGGCGCAAGCTGCTTGCTCAGAAGAGCCATGACAATGCTC
W S F L S W R R K L L A Q K S H D N A Q 300

FIG. 3d

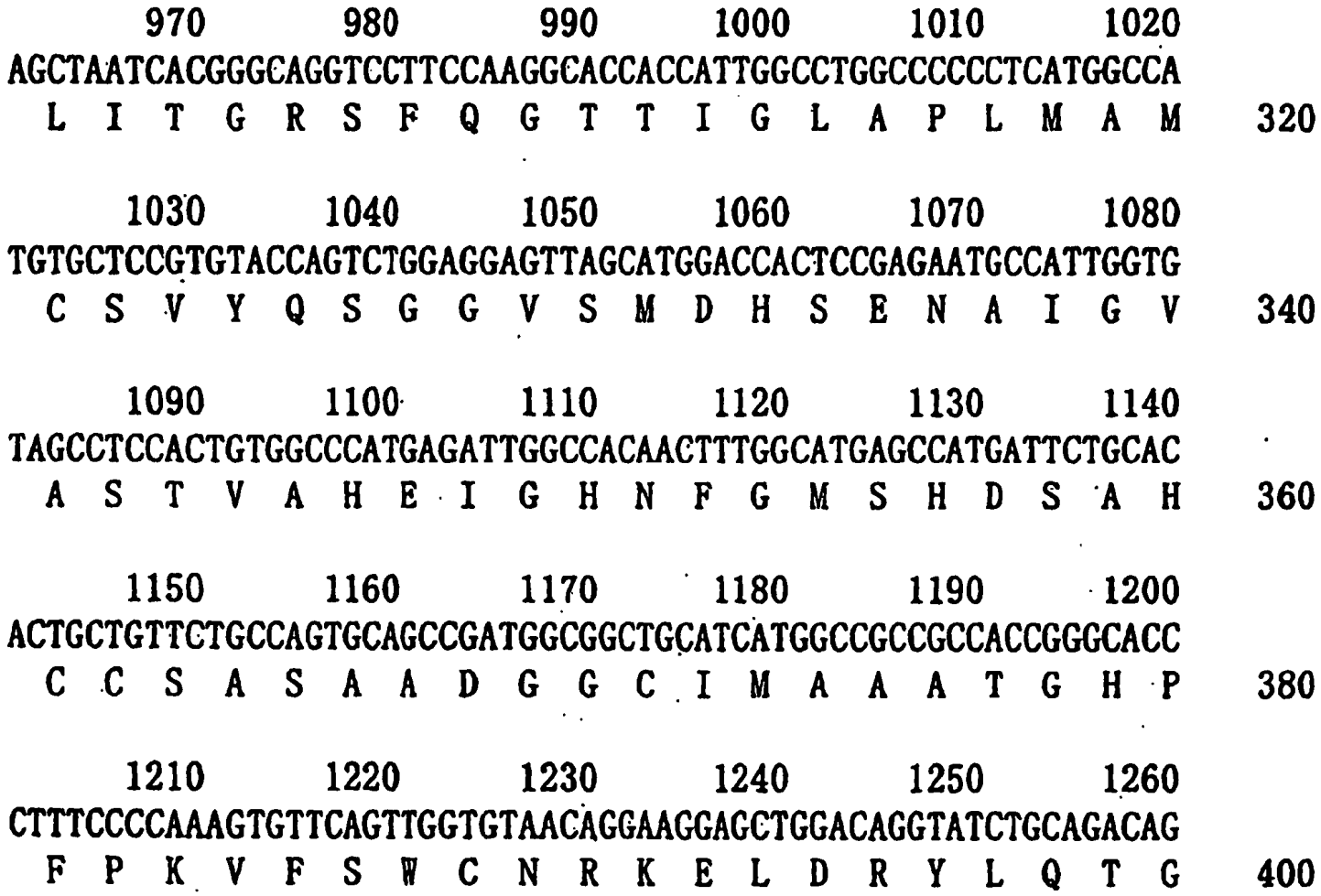

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FIG. 3e

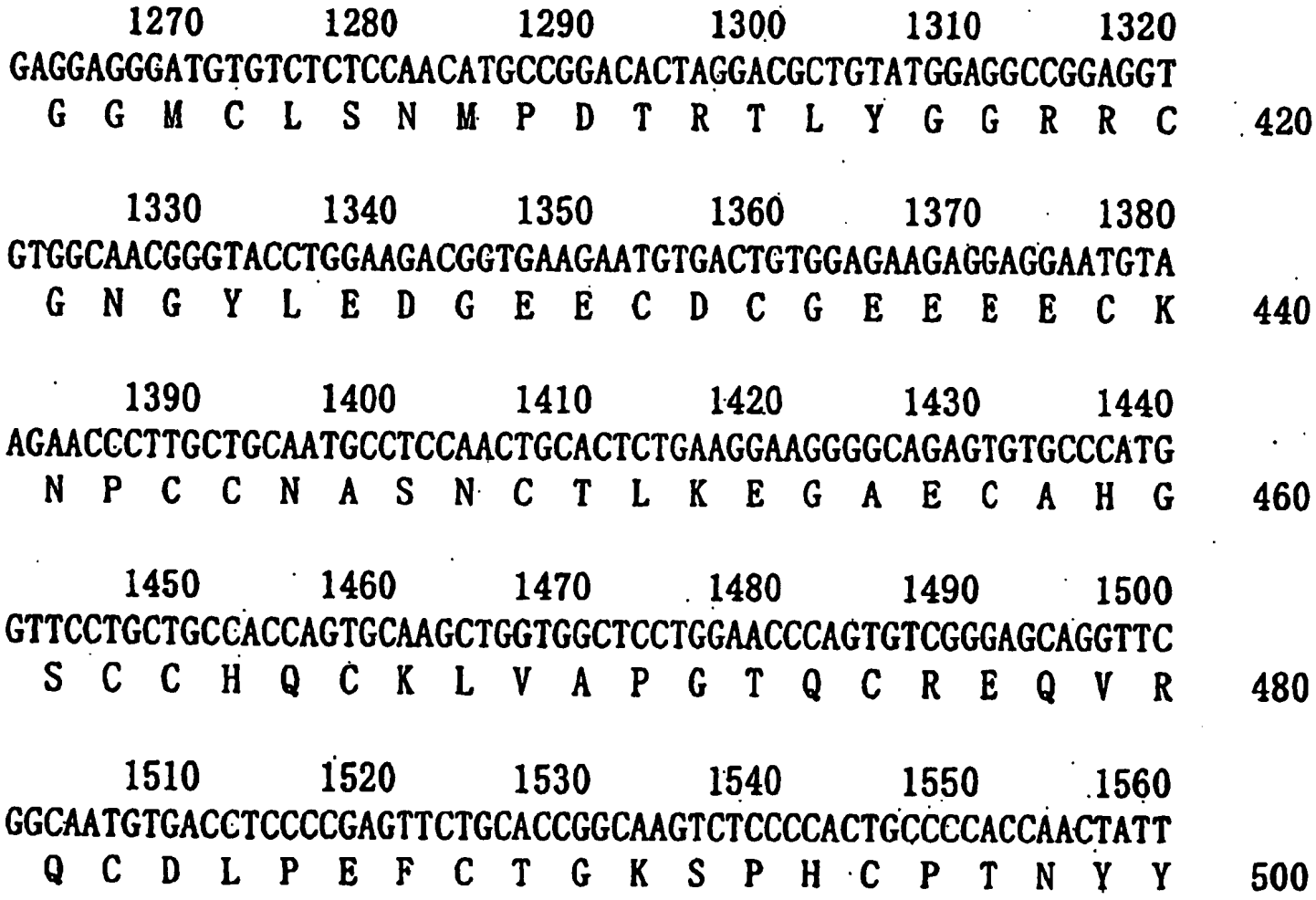

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FIG. 3f

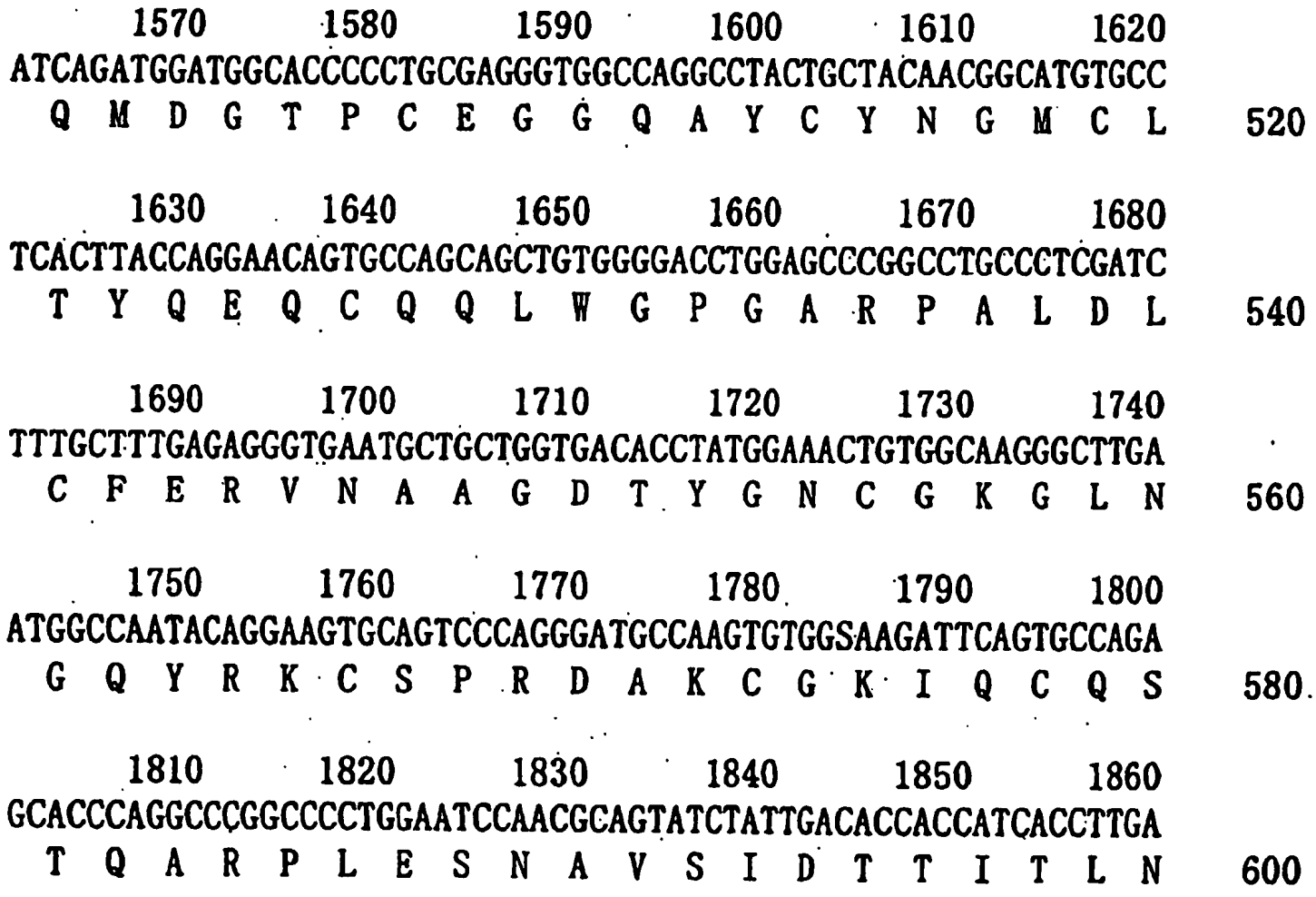

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FIG. 3g

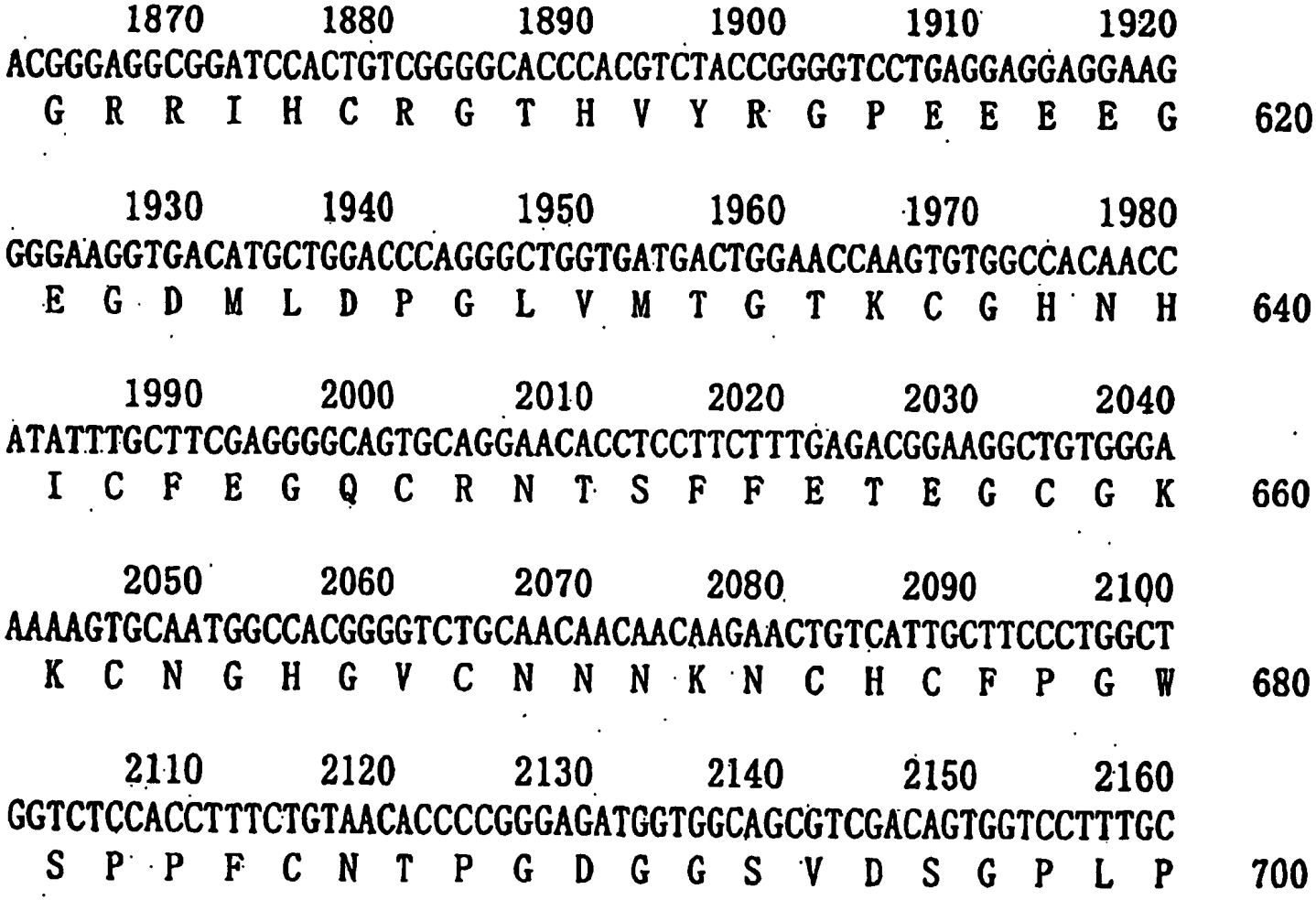
1870 1880 1890 1900 1910 1920
ACGGGAGGCGGATCCACTGTCGGGGCACCCACGTCTACCGGGGTCCTGAGGAGGAGGAAG
G R R I H C R G T H V Y R G P E E E E G 620
1930 1940 1950 1960 1970 1980
GGGAAGGTGACATGCTGGACCCAGGGCTGGTGATGACTGGAACCAAGTGTGGCCACAACC
E G D M L D P G L V M T G T K C G H N H 640
1990 2000 2010 2020 2030 2040
ATATTTGCTTCGAGGGGCAGTGCAGGAACACCTCCTTCTTTGAGACGGAAGGCTGTGGGA
I C F E G Q C R N T S F F E T E G C G K 660
2050 2060 2070 2080 2090 2100
AAAAGTGCAATGGCCACGGGGTCTGCAACAACAACAAGAACTGTCATTGCTTCCCTGGCT
K C N G H G V C N N N K N C H C F P G W 680
2110 2120 2130 2140 2150 2160
GGTCTCCACCTTTCTGTAACACCCCGGGAGATGGTGGCAGCGTCGACAGTGGTCCTTTGC
S P P F C N T P G D G G S V D S G P L P 700

FIG. 3h

```
      2170       2180       2190       2200       2210       2220
CCCCTAAGAGTGTGGGTCCCGTGATCGCTGGGGTGTTTTCAGCTCTCTTCGTGTTGGCAG
  P  K  S  V  G  P  V  I  A  G  V  F  S  A  L  F  V  L  A  V    720

      2230       2240       2250       2260       2270       2280
TTCTGGTGCTACTGTGTCACTGCTACAGACAGAGCCACAAACTGGGCAAACCCTCGGCTC
  L  V  L  L  C  H  C  Y  R  Q  S  H  K  L  G  K  P  S  A  L    740

      2290       2300       2310       2320       2330       2340
TCCCTTTCAAGCTGCGGCATCAGTTCAGTTGTCCCTTCAGGGTATCTCAGAGTGGTGGAA
  P  F  K  L  R  H  Q  F  S  C  P  F  R  V  S  Q  S  G  G  T    760

      2350       2360       2370       2380       2390       2400
CTGGCCATGCCAACCCAACTTTCAAGTTGCAGACCCCCCAGGGCAAGCGAAAGGTGACTA
  G  H  A  N  P  T  F  K  L  Q  T  P  Q  G  K  R  K  V  T  N    780

      2410       2420       2430       2440       2450       2460
ACACCCCTGAATCCCTCCGGAAGCCGTCCCACCCCCCTCTCCGGCCCCCTCCAGACTACC
  T  P  E  S  L  R  K  P  S  H  P  P  L  R  P  P  P  D  Y  L    800
```


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FIG. 3i

```
      2470       2480       2490       2500       2510       2520
TGCGCGTTGAATCGCCACCTGCACCATTGTCGGCACATCTGAACAGGGCTGCTGGGAGCT
  R  V  E  S  P  P  A  P  L  S  A  H  L  N  R  A  A  G  S  S    820

      2530       2540       2550       2560       2570       2580
CCCCAGAAGCTGGGGCTCGAATAGAAAGAAAGGAGTCAGCCAGGAGGCCTCCCCCAAGCC
  P  E  A  G  A  R  I  E  R  K  E  S  A  R  R  P  P  P  S  R    840

      2590       2600       2610       2620       2630       2640
GACCCATGCCCCCTGCACCTAACTGCCTACTGTCCCAGGACTTCTCCAGGCCTCGACCAC
  P  M  P  P  A  P  N  C  L  L  S  Q  D  F  S  R  P  R  P  P    860

      2650       2660       2670       2680       2690       2700
CTCAGAAGGCACTCCCAGCCAATCCGGTGCCAGGCCAAAGGACCGGTCCCAGGTCAGGAG
  Q  K  A  L  P  A  N  P  V  P  G  Q  R  T  G  P  R  S  G  G    880

      2710       2720       2730       2740       2750       2760
GCACCTCCCTGCTTCAGCCCCCTACTTCTGGTCCTCAGCCCCCCAGGCCTCCAGCAGTGC
  T  S  L  L  Q  P  P  T  S  G  P  Q  P  P  R  P  P  A  V  P    900
```


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FIG. 3j

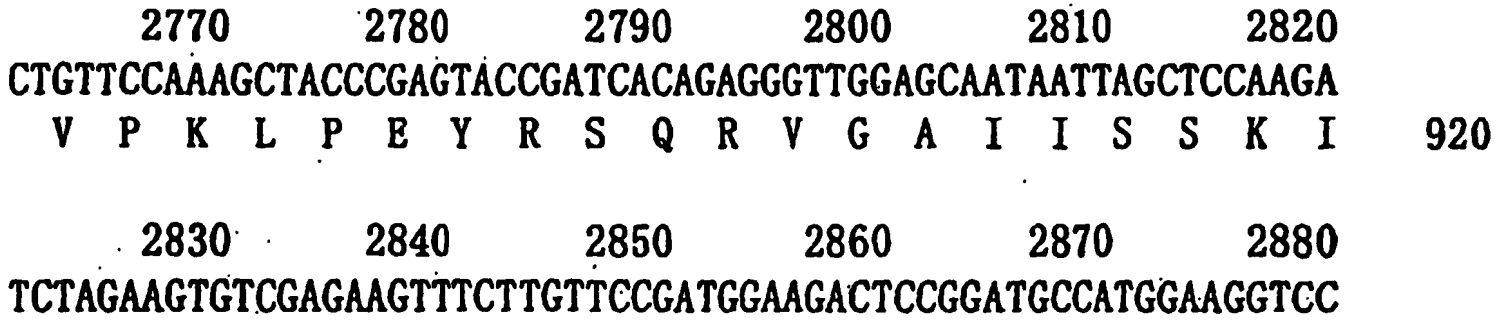

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FIG. 4a

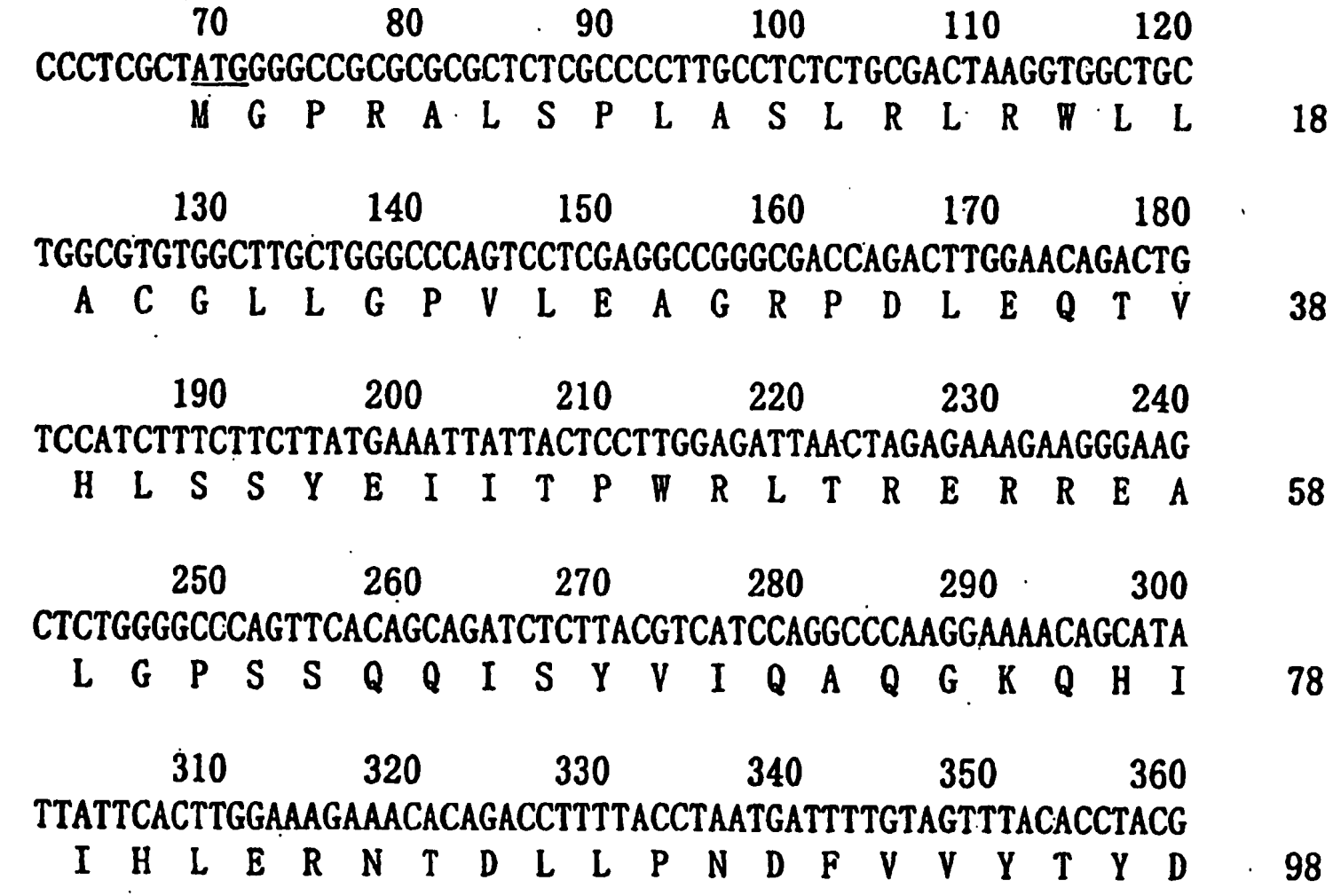

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FIG. 4b

```
      370        380        390        400        410        420
ACAAGGAAGGCTCCCTACTCTCTGACCATCCCAACGTACAGAGCCATTGTCACTATCGAG
  K  E  G  S  L  L  S  D  H  P  N  V  Q  S  H  C  H  Y  R  G    118

      430        440        450        460        470        480
GCTATGTGGAGGGAGTGCAGAATTCCGCGGTTGCTGTGAGCGCCTGCTTTGGACTCAGAG
  Y  V  E  G  V  Q  N  S  A  V  A  V  S  A  C  F  G  L  R  G    138

      490        500        510        520        530        540
GCTTGCTGCATTTGGAGAATGCCAGTTTTGGAATTGAACCTCTGCACAACAGCTCACACT
  L  L  H  L  E  N  A  S  F  G  I  E  P  L  H  N  S  S  H  F    158

      550        560        570        580        590        600
TTGAGCACATATTTTACCCCATGGATGGCATCCACCAGGAGCCTCTGAGATGTGGAGTCT
  E  H  I  F  Y  P  M  D  G  I  H  Q  E  P  L  R  C  G  V  S    178

      610        620        630        640        650        660
CTAACAGGGACACAGAGAAGGAAGGCACACAGGGGGATGAGGAGGAGCATCCGAGTGTCA
  N  R  D  T  E  K  E  G  T  Q  G  D  E  E  E  H  P  S  V  T    198
```


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FIG. 4c

```
      670        680        690        700        710        720
CTCAGCTGCTGCGCAGAAGAAGAGCTGTTCTACCACAGACCCGCTATGTGGAGCTGTTCA
  Q  L  L  R  R  R  R  A  V  L  P  Q  T  R  Y  V  E  L  F  I    218

      730        740        750        760        770        780
TTGTTGTAGACAAGGAAAGGTACGACATGATGGGACGGAACCAGACTGCTGTGAGAGAAG
  V  V  D  K  E  R  Y  D  M  M  G  R  N  Q  T  A  V  R  E  E    238

      790        800        810        820        830        840
AGATGATTCGCTTAGCAAACTACCTGGATAGCATGTACATCATGTTAAACATTCGAATTG
  M  I  R  L  A  N  Y  L  D  S  M  Y  I  M  L  N  I  R  I  V    258

      850        860        870        880        890        900
TGCTGGTTGGACTAGAAATTTGGACAGACAGAAATCCTATCAATATAATTGGAGGAGCTG
  L  V  G  L  E  I  W  T  D  R  N  P  I  N  I  I  G  G  A  G    278

      910        920        930        940        950        960
GAGATGTGCTGGGCAACTTTGTTCAGTGGCGGGAAAAGTTCCTTATAACTCGTCGGAGAC
  D  V  L  G  N  F  V  Q  W  R  E  K  F  L  I  T  R  R  R  H    298
```


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FIG. 4d

```
          970        980        990       1000       1010       1020
ACGACAGTGCACAGTTGGTTTTGAAGAAAGGCTTTGGTGGAACTGCAGGAATGGCGTTTG
  D  S  A  Q  L  V  L  K  K  G  F  G  G  T  A  G  M  A  F  V    318

          1030       1040       1050       1060       1070       1080
TAGGAACAGTATGTTCAAGGAGCCACGCAGGTGGGATCAATGTGTTTGGGCAAATCACTG
  G  T  V  C  S  R  S  H  A  G  G  I  N  V  F  G  Q  I  T  V    338

          1090       1100       1110       1120       1130       1140
TGGAGACATTTGCATCCATTGTTGCTCATGAATTGGGGCATAACCTTGGAATGAATCATG
  E  T  F  A  S  I  V  A  H  E  L  G  H  N  L  G  M  N  H  D    358

          1150       1160       1170       1180       1190       1200
ATGATGGGAGAGAGTGTTTCTGTGGAGCAAAGAGCTGTATCATGAATTCAGGAGCATCCG
  D  G  R  E  C  F  C  G  A  K  S  C  I  M  N  S  G  A  S  G    378

          1210       1220       1230       1240       1250       1260
GGTCCAGAAACTTTAGCAGTTGCAGTGCGGAGGACTTTGAGAAGTTAACGTTGAATAAGG
  S  R  N  F  S  S  C  S  A  E  D  F  E  K  L  T  L  N  K  G    398
```


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FIG. 4e

```
      1270       1280       1290       1300       1310       1320
GAGGAAGCTGCCTGCTTAACATCCCGAAGCCTGACGAAGCCTACAGCGCGCCCTCCTGTG
  G  S  C  L  L  N  I  P  K  P  D  E  A  Y  S  A  P  S  C  G    418

      1330       1340       1350       1360       1370       1380
GTAATAAGCTGGTGGACCCTGGAGAGGAGTGTGACTGCGGCACAGCGAAGGAGTGTGAGG
  N  K  L  V  D  P  G  E  E  C  D  C  G  T  A  K  E  C  E  V    438

      1390       1400       1410       1420       1430       1440
TGGACCCATGCTGTGAAGGAAGCACTTGTAAGCTCAAGTCATTTGCTGAGTGTGCATATG
  D  P  C  C  E  G  S  T  C  K  L  K  S  F  A  E  C  A  Y  G    458

      1450       1460       1470       1480       1490       1500
GCGACTGTTGTAAAGATTGCCAGTTCCTTCCAGGAGGCTCCATGTGCAGAGGGAAGACCA
  D  C  C  K  D  C  Q  F  L  P  G  G  S  M  C  R  G  K  T  S    478

      1510       1520       1530       1540       1550       1560
GTGAGTGTGATGTTCCTGAGTACTGCAACGGTTCCTCTCAGTTCTGCCCGCCAGATGTCT
  E  C  D  V  P  E  Y  C  N  G  S  S  Q  F  C  P  P  D  V  F    498
```


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FIG. 4f

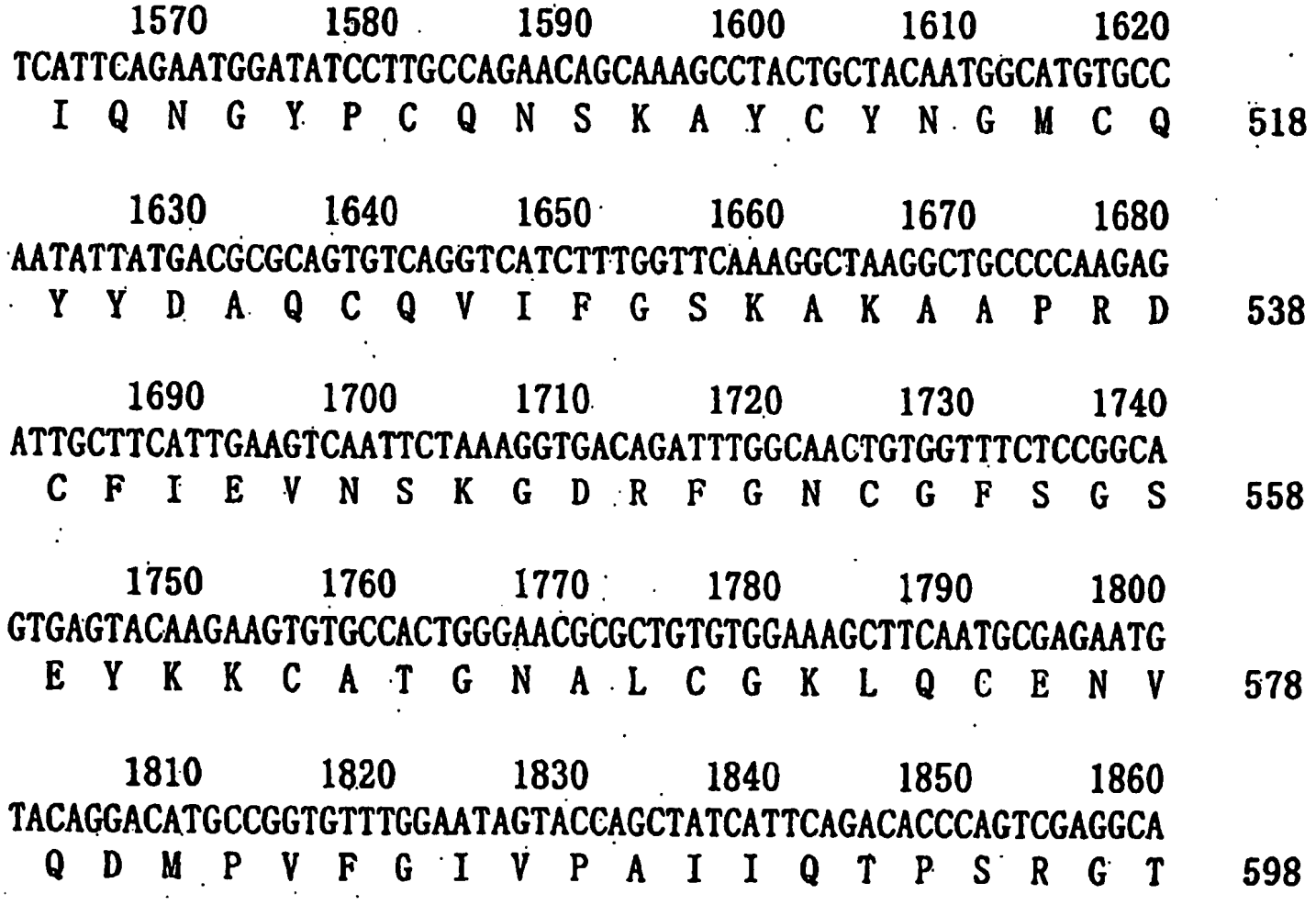
1570 1580 1590 1600 1610 1620
TCATTCAGAATGGATATCCTTGCCAGAACAGCAAAGCCTACTGCTACAATGGCATGTGCC
I Q N G Y P C Q N S K A Y C Y N G M C Q 518
1630 1640 1650 1660 1670 1680
AATATTATGACGCGCAGTGTCAGGTCATCTTTGGTTCAAAGGCTAAGGCTGCCCCAAGAG
Y Y D A Q C Q V I F G S K A K A A P R D 538
1690 1700 1710 1720 1730 1740
ATTGCTTCATTGAAGTCAATTCTAAAGGTGACAGATTTGGCAACTGTGGTTTCTCCGGCA
C F I E V N S K G D R F G N C G F S G S 558
1750 1760 1770 1780 1790 1800
GTGAGTACAAGAAGTGTGCCACTGGGAACGCGCTGTGTGGAAAGCTTCAATGCGAGAATG
E Y K K C A T G N A L C G K L Q C E N V 578
1810 1820 1830 1840 1850 1860
TACAGGACATGCCGGTGTTTGGAATAGTACCAGCTATCATTCAGACACCCAGTCGAGGCA
Q D M P V F G I V P A I I Q T P S R G T 598

FIG. 4g

```
      1870       1880       1890       1900       1910       1920
CCAAATGCTGGGGTGTGGATTTCCAGCTTGGTTCCGACGTTCCAGACCCAGGGATGGTGA
  K  C  W  G  V  D  F  Q  L  G  S  D  V  P  D  P  G  M  V  N    618

      1930       1940       1950       1960       1970       1980
ATGAAGGCACCAAATGTGATGCTGGCAAGATTTGCAGGAATTTTCAGTGTGTAAATGCTT
  E  G  T  K  C  D  A  G  K  I  C  R  N  F  Q  C  V  N  A  S    638

      1990       2000       2010       2020       2030       2040
CTGTCCTGAATTATGACTGTGACATTCAGGGAAAATGTCATGGCCATGGGGTATGTAACA
  V  L  N  Y  D  C  D  I  Q  G  K  C  H  G  H  G  V  C  N  S    658

      2050       2060       2070       2080       2090       2100
GCAATAAGAATTGTCACTGTGAAGATGGCTGGGCTCCCCCACACTGTGACACCAAAGGAT
  N  K  N  C  H  C  E  D  G  W  A  P  P  H  C  D  T  K  G  Y    678

      2110       2120       2130       2140       2150       2160
ATGGAGGAAGCGTGGACAGCGGGCCGACGTATAATGCAAAGAGCACAGCACTGAGGGACG
  G  G  S  V  D  S  G  P  T  Y  N  A  K  S  T  A  L  R  D  G    698
```


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FIG. 4h

```
      2170       2180       2190       2200       2210       2220
GGCTTCTGGTCTTCTTCTTCCTAATCGTCCCCCTTGTTGCGGCTGCCATTTTCCTCTTTA
  L  L  V  F  F  F  L  I  V  P  L  V  A  A  A  I  F  L  F  I    718

      2230       2240       2250       2260       2270       2280
TCAAGAGAGATGAACTACGGAAAACCTTCAGGAAGAAGAGATCACAAATGTCAGATGGCA
  K  R  D  E  L  R  K  T  F  R  K  K  R  S  Q  M  S  D  G  R    738

      2290       2300       2310       2320       2330       2340
GAAATCAAGCAAACGTCTCTAGACAGCCAGGAGATCCTAGTATCTCCAGACCACCAGGGG
  N  Q  A  N  V  S  R  Q  P  G  D  P  S  I  S  R  P  P  G  G    758

      2350       2360       2370       2380       2390       2400
GCCCAAATGTCTCCAGACCACCAGGGGGCCCAGGTGTCTCCAGACCACCAGGGGGCCCAG
  P  N  V  S  R  P  P  G  G  P  G  V  S  R  P  P  G  G  P  G    778

      2410       2420       2430       2440       2450       2460
GTGTCTCCAGACCACCAGGGGGCCCAGGTGTCTCCAGACCGCCACCTGGGCATGGAAACA
  V  S  R  P  P  G  G  P  G  V  S  R  P  P  P  G  H  G  N  R    798
```


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FIG. 4i

```
      2470       2480       2490       2500       2510       2520
GATTCCCAGTACCAACCTACGCCGCCAAGCAGCCTGCGCAGTTCCCGTCAAGGCCACCTC
  F  P  V  P  T  Y  A  A  K  Q  P  A  Q  F  P  S  R  P  P  P    818

      2530       2540       2550       2560       2570       2580
CACCACAACCGAAAATATCTTCTCAGGGAAACTTGATTCCGGCTCGGCCCGCTCCTGCAC
  P  Q  P  K  I  S  S  Q  G  N  L  I  P  A  R  P  A  P  A  P    838

      2590       2600       2610       2620       2630       2640
CTCGTTTATATAGCTCCCTCACCTGATAGTAGAATATTAGAATCTTATTTTTTAAATGTC
  P  L  Y  S  S  L  T    845
```

FIG. 5a

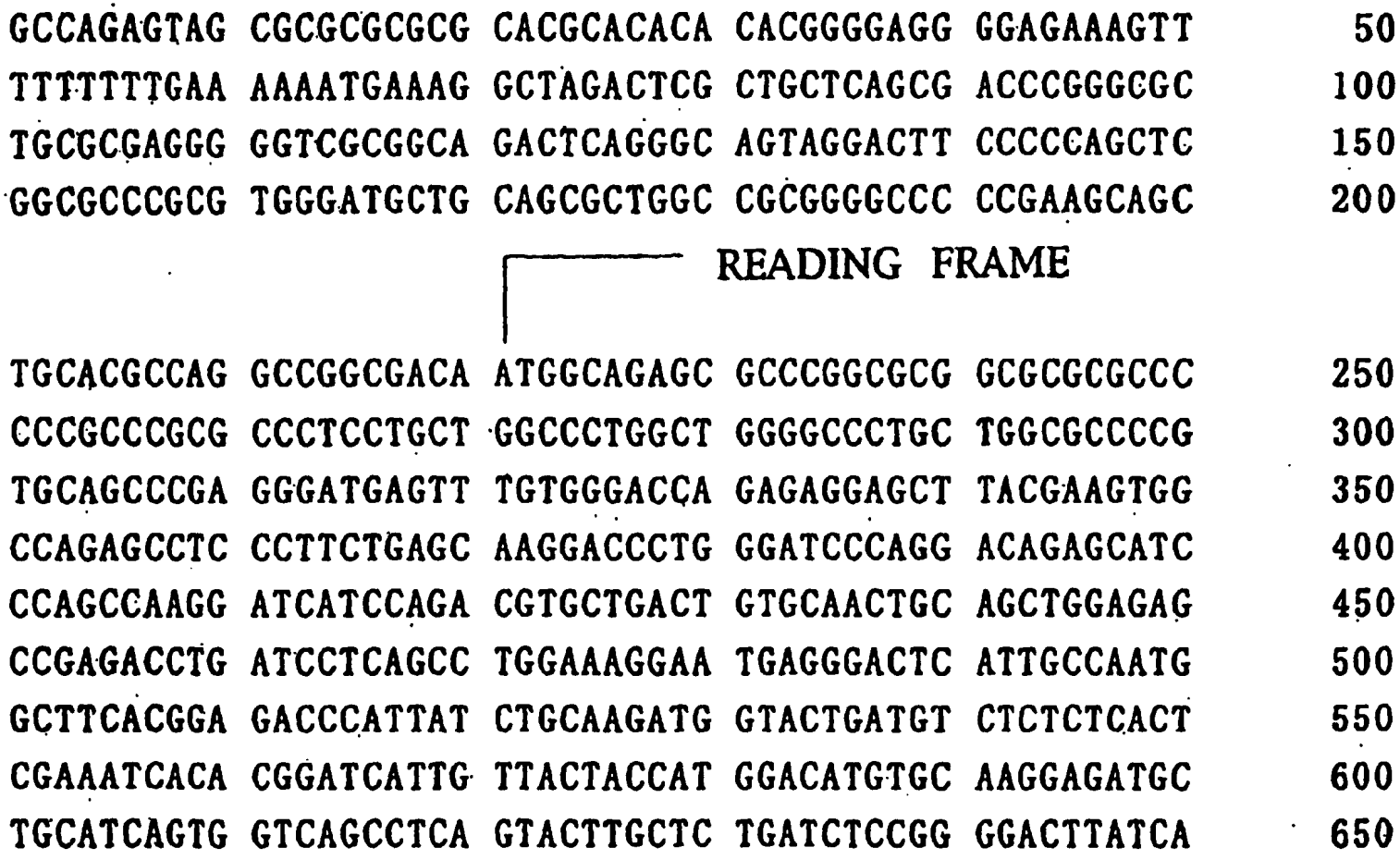

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FIG. 5b

```
TGTTTGAAAA TAAAACGTAC AGCTTAGAGC CAATGAAAAA CACCACTGAC      700
AGCTACAAAC TCGTCCCAGC TGAGAGCATG ACGAACATCC AAGGGCTGTG      750
TGGGTCACAG CATAACAAGT CCAACCTCAC CATGGAAGAT GTCTCCCCTG      800
GAACCTCTCA AATGCGGGCA AGAAGGCATA AGAGAGAGAC CCTTAAGATG      850
ACCAAGTACG TAGAGCTGGT TATTGTGGCA GACAACAGAG AGTTTCAGAG      900
GCAAGGAAAA GACCTGGAGA AAGTTAAGCA GCGATTAATA GAGATCGCCA      950
ATCACGTTGA CAAGTTTTAC AGACCACTGA ACATCCGGAT CGTGCTGGTA     1000
GGAGTGGAAG TGTGGAATGA CATCGACAAA TGCTCTATAA GCCAGGACCC     1050
ATTCACCAGG CTCCATGAGT TTCTAGACTG GAGAAAGATA AAGCTTCTAC     1100
CTCGAAAATC CCACGACAAT GCTCAGCTTA TCAGTGGGGT TTATTTCCAA     1150
GGAACCACCA TCGGCATGGC ACCCATCATG AGCATGTGCA CTGCAGAACA     1200
GTCTGGAGGA GTTGTCATGG ACCATTCAGA CAGCCCCCTT GGTGCCGCAG     1250
TGACCTTGGC ACATGAGCTG GGCCACAACT TCGGGATGAA CCATGACACA     1300
CTGGAGAGGG GCTGCAGCTG CAGAATGGCC GCAGAGAAAG GAGGCTGCAT     1350
CATGAACCCG TCCACGGGGT TCCCATTCCC CATGGTGTTC AGCAGCTGCA     1400
```

FIG. 5c

```
GCAGGAAGGA CCTGGAGGCT AGCCTGGAGA AGGGCATGGG GATGTGCCTC     1450
TTCAACCTAC CAGAGGTCAA GCAGGCCTTT GGGGGCCGGA AGTGTGGAAA     1500
TGGCTATGTG GAAGAGGGAG AAGAGTGTGA CTGCGGAGAA CCGGAGGAAT     1550
GCACGAATCG CTGCTGTAAC GCTACCACCT GTACTCTGAA GCCAGATGCT     1600
GTGTGCGCGC ACGGGCAGTG CTGTGAAGAC TGTCAGCTGA AGCCTCCAGG     1650
AACTGCATGC AGGGGCTCCA GCAACTCCTG TGACCTCCCA GAATTCTGCA     1700
CAGGGACTGC CCCTCACTGT CCAGCCAATG TGTACCTACA TGATGGCCAC     1750
CCGTGTCAGG GCGTGGATGG TTACTGCTAC AACGGCATCT GCCAGACCCA     1800
TGAGCAGCAG TGTGTCACGC TCTGGGGACC AGGTGCTAAA CCGGCTCCTG     1850
GCATCTGCTT TGAGCGAGTC AACTCTGCAG GAGATCCTTA TGGTAACTGT     1900
GGCAAAGACT CCAAGAGCGC CTTCGCCAAA TGTGAGCTGA GAGATGCCAA     1950
GTGTGGGAAA ATCCAGTGTC AAGGTGGTGC AAGCCGACCT GTCATTGGTA     2000
CCAATGCTGT TTCCATAGAA ACAAATATCC CACAGCAGGA AGGAGGTCGG     2050
ATTCTGTGCC GGGGGACCCA TGTGTACTTG GGTGATGACA TGCCAGACCC     2100
AGGGCTTGTG CTTGCAGGAA CAAAGTGTGC AGAAGGAAAA ATCTGCCTCA     2150
```


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FIG. 5d

```
ATCGTCGATG TCAGAATATC AGTGTCTTCG GCGTTCACAA GTGTGCCATG     2200
CAGTGCCACG GCCGAGGGGT ATGTAACAAC AGGAAGAATT GCCACTGTGA     2250
AGCCCACTGG GCTCCACCCT TCTGTGACAA GTTTGGCTTT GGAGGAAGCA     2300
CAGACAGTGG TCCCATCAGG CAAGCAGATA ACCAGGGCTT GACTGTAGGA     2350
ATCCTGGTGA GCATCCTGTG TCTGCTTGCT GCTGGATTTG TGGTGTATCT     2400
CAAAAGGAAG ACGTTGATGC GGCTGCTGTT CACACATAAA AAAACCACCA     2450
TGGAAAAGCT AAGGTGTGTG CACCCTTCCC GGACACCCAG TGGCCCTCAC     2500
CTTGGCCAGG CTCACCACAC CCCCGGGAAA GGCCTGCTGA TGAACCGGGC     2550
ACCACATTTC AATACCCCCA AGGACAGGCA CTCGCTGAAA TGCCAGAACA     2600
TGGACATCAG CAGGCCCCTC GACGCTCGAG CCGTCCCACA GCTTCAGTCA     2650
CCTCAGCGAG TGCTCCTGCC TCTCCACCAG ACCCCACGTG CACCCAGTGG     2700
CCCTGCCAGG CCCCTGCCCG CCAGTCCTGC AGTCAGGCAG GCCCAGGGCA     2750
TTCGAAAACC CAGTCCTCCT CAGAAGCCTC TGCCTGCTGA TCCACTGAGC     2800
AGGACTTCTC GGCTCACTAG TGCCTTGGTG AGGACCCCAG GGCAGCAGGA     2850
```


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FIG. 5e

READING FRAME

```
ACCTGGGCAC CGCCCAGCCC CCATCAGACC TGCCCCTAAG CATCAAGTAC    2900
CCAGACCTTC CCACAATGCC TATATCAAGT GAGAAGCCAG CCCAGACCGG    2950
TCCTCAACAG TGAAGACAGA AGTTTGCACT ATCTTCAGCT CCATTGGAGT    3000
TGTTGTTGTA CCAACTTTCC GAGTTTCTAA AGTGTTTAAA ACACCATTCT    3050
CTCCAGACCC TGGAGCCACT GCCATCGGTG CTGTGCTGTG GTGCTTTGTG    3100
TACTTGCTCA GGAACTTGTA AGTTATTAAT TTATGCAGAG TGTCTATTAC    3150
TGCGCAGGGC GCCGTAGCAG GCATTTGTAC CATCACAGGG CTTTTCTACA    3200
GAAGGAAGGC TCCTCGTGCT TTTGTTTTTC TGGAGGACTT GAAATACCCT    3250
GCTTGATGGG ACCTAAGATG AGATGTTTAC TTTCTATTCA AGGCCTTATC    3300
GGAAAATAGC TCCCCACCTT CCCAAGGCTG TTATGGTACC AGACACACAG    3350
CTCAGGACAC CCCAGGGAGA ACCTGGCATG GGTTTTCTTT GTTTGCTTTC    3400
ATTTTATCTT TTATATTTTG GTATCCCTAT CTTGGGTTGT AGCCAGGGCC    3450
TTCAGGAAGG TCTTGGGCCA CTGCATGCTA ATGGCCTTCA GGTCCTGCAC    3500
```


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FIG. 5f

```
CCTGAAGCTC TCAGACAACA AGTAGGATCT GCTTTCTAGC CAGCAGCTTT     3550
GGAGAGAACC TGGGGTACTG AAAAGAAGGT TTGGGGTGTG GTTATACCAG     3600
GATGGAGACT GGAATCCTAA TCTGGGCAAA CATCTGACCT TGAGCTGAGC     3650
AGCCATGAGC ACCTCTAGGA AGCAAGGACG GCTGAGGTGC TGCACAAGGC     3700
TCTGCTTTGA GAGCTGGCAG GGGCTTCTCT CTGGCTGCCC TTTGCAGAGT     3750
GCTAGCTGGC ATGGCATGTT GTTTACATCG GGAACAGTGG TGTTTCTACA     3800
AGAAAGCCAC TGCCTGGGCA CTGCAGACCT CCGTCTCCTG CCCATTTAGA     3850
GCTAAGCAAA TTACCACATT GTCTTCTGGA CTGTAATACA ATGACCCTGT     3900
GTTCTGACAG ATAGAGGAGG CTTTCTATGG AACCATAACT ATTTTCANAT     3950
GTGAACTAGT AACCAGATCT AGTCGATCAA CTCTGGAGAT AGAAATCTCC     4000
TTTTTACTGC AAGGCTCGAC TTATTAAAAA TTAGGCAGAA TCCATATGCT     4050
TGCAAAAGCT ATAACCACGT GGAATGCTCT TCTCATGGCA CAGCCTGAGT     4100
CTGGTATCCT TATTAGTAGC CATTGGACAA AGCACCCAAA GTTACCTGTG     4150
TGTTCTCTTC AAGGCATCCT AATTTCTTCA GCATAGAGAG ACTCGGTCTT     4200
CCTCACATTC TGAACATACC TATCAATGAC TAAGNCAGCA AGGCAATCCG     4250
```


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FIG. 5g

```
TTTCCGAATA CTGAGTTGCT CACGGNAAGG CAACCTCAGC CCAGGNAAAC     4300
TTTTTTCCTC TGNTCTTTCA GTATGTGACT GGGGAGCTAC CTTCAGAAGC     4350
AAATTTTCAA GGTGGNCTCA ACCCCATNGG ATGAAAGNTA TTTTTTTAAA     4400
AAATAATTAA TGGTAATGCC AGAGGGCTTT CCTGGCNTCC AGATNGGGGC     4450
GTAGGNTTGA CTAGCTTTCA CGACAGAAGG TAAATGACAG CAGTCCTCTA     4500
CCTCGTCTGA CTGCTTTAAG ATCAAGGCTT CTTTGGAAGG GTAACTAACA     4550
TTAATGGCTG GCCTGTGCCT TGAAGCAGAA GGGAAAATAC AGATAAGGAA     4600
TTTGGTTTGC TTTCTAGAAT CCAAAACTGT ATCCAGCATT GGGAAGCATG     4650
GTCTTCATGA CTGGGTAAAT AAATCCACGT CACAGATGCA TAAAAGAATA     4700
ACTCTTATGA CATGCCTCTT TTTGTGGCAC AGAGACAATA TTGCTGCCAC     4750
TGAGATGCAT ACAAAATTTC TGTAACTGAT ATGTCATTCA GTAGTTGTAT     4800
TAAGGCCAAA CATCCACAAC TGTAAAGACT TATAGAGTTG TGTGGGCGTT     4850
GTCTTGTGAG ACACACAAAG CCTCAGCTGA AGCGTATGAG CTCCTCCTCC     4900
AGGTGGGAGT GATGGGGAGG CTAGAAACAC ACAAAGACAA CAGAAGAGCT     4950
TTGGTTTGGG GGGGGTGCAG AGAGAGTGTG GTTTAGAGGA AGTTGGAGCC     5000
```

FIG. 5h

```
ATGATCTTCT GCCATCTCCC CAGTGTCCAC TAAGGATGCC GATGGTGCCT    5050
TACCAGCTGT GCAGTGCTGG CTGCTTGCTT TTACAGAGCC ATGCATTCAT    5100
TTCTGAATAA GAACATATTT AATCCTGAAA TTCCCTTACA GGACAGACAG    5150
TGTTACTAAA GGAATTCCTC TAAGATACAG TAGTTGTCAA TTAAAGCATA    5200
TTTAGCAGTA ACTTCAATTT TAACAAAATT GGGACCCAAT AGCCAGCATG    5250
AGGGTTCTTT GACAGAGGGT AGTTTCTCTC TCCCTTTCTC CATCCTTCAA    5300
ATGACAAGAC GTCAAAACTA ATACAGTTCA TTTGCAGTCC ATCTCATGCT    5350
TATACATACT AGAGGTATGA CTAAAGTTGG TTGAGTCATG GGAGACCATC    5400
CCTGAGAAAG TCCAGTCGGT CAAGAGCCTT GCCAGGTGGC GTGGCTGGAC    5450
GTCCTCCTTT TGTTCCTGCA CTGAGGAATA GTTATAGGTT ATGTGACCCC    5500
ACTTCACAGG CAAGTGGGAG GCGAACCTTG CAGGCATGCC CCTTAAAAGC    5550
TGGTCTCAGA CCTACAATAG TCCTGAGTCT GTTTTCCCAG CACACAGAGA    5600
GCAACAATGC AGTTTTCCAT TTCAAAATAT GCATGCCGAG TTTGCGCTCT    5650
GTGTGAGTGT TTCCAGGTTA CACATATGGG ATGACATCAC AGAAACCACA    5700
CAAGCAACAA ATTAAATTCT ACGGGAAGAA ATCCTCCTGA CTGGTCTCTG    5750
```


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FIG. 5i

```
AGGAGACATT TTTATGCCTT CTTAACTTTA TTAGGAACTC TCAGGCTGAA    5800
GCTAGGGGTC ATTGTCCCCC AACAAATCAA TACAAAGCCA TCAATGNACT    5850
CTCGAAGAAC TGCCAAACCC TGATCTGTGT GAATGTTCTC AGGAGCCTGT    5900
GATCCCCATG GTGCTANAAA GAGGCTGGAG CTGGGCCAAC AAGAAGGCCT    5950
AAGAGTCCTC CTGCCTCTCA GCAGATGTTT ACTGAGCACT CTGAGCCAGA    6000
AGCACCCCGA CAACCAGGAG GACGATNGCT GGGCAGTAGG GCGCCCAGCC    6050
ACTTGCAGCT CTTTCCTCTG AGGCCCGCTT TGTGTTTTAA TTCCCTTCTG    6100
TCAGGCCCCA ANCAGNGGAC ACTGTCCTAT AGACCTCCCT CTNAGTTTTC    6150
AGACGGCCTA AGCCATACAC AAATGCCCCA GACTAAGAAA CACCAATACN    6200
TCCCAGCAGT CCCCAAGAAC TGGTTTTTAA ACACTATGAC AAGTAGAAGA    6250
GGGTGTCACA GAGGCCATTT TTTTTCTTTT CTTTCCACTC ATACTGGAAC    6300
CTAGGTCCTC TCTCTACACT CCTAGTTCCT TTACACAACT CGGCAGTGGC    6350
TCCATTACAC CAAGGACACA GAAAAACACA GGTACCGATT TGCCTTCCTC    6400
TCCTGCCAAT CACAAGTGCC TTACTCTGAC CAGACCCATG ACAAAACCTC    6450
TGTCATCCAA GAGAGCCAAC TCTCTACCTT TGTTACTACT TCAAGCCAAT    6500
```

FIG. 5j

```
GTGGTAACTG CTAACCTTCA AGGGTCACCT AAACAGTATA GTCCAACCTT    6550
CACCAGGACC ATAGCACAGA GCAACCTCCA GNACACACAC ACACACACAC    6600
CTTGAATCTA TCCCACAGCA TATCAACCCA CAGTGACCTC CCTCCCACCG    6650
CCTTGTTCTA ATTACAAGGT GAAGATGGCC ATAGAAAATC AAGTTAGCAC    6700
TAATTACAAA ATGCTTTTGA TGCAACCTGA ATTTCCCAAT GGCACCTATT    6750
GCTTTGAAAC TCTGATGAGT TAAGTCATGC TCTGGGAGCT GTGAGCCCCA    6800
TGCTCAGATC CACTGGGCAG GGGGGACTCC TTGCAGGAGA CATGGGCACA    6850
CATATGAATG TACCATTTCC ATGCCTTTTG TGGAGTACAG ACATATAAAC    6900
ATAAATACTT CCATT                                         6915
```

FIG. 6a

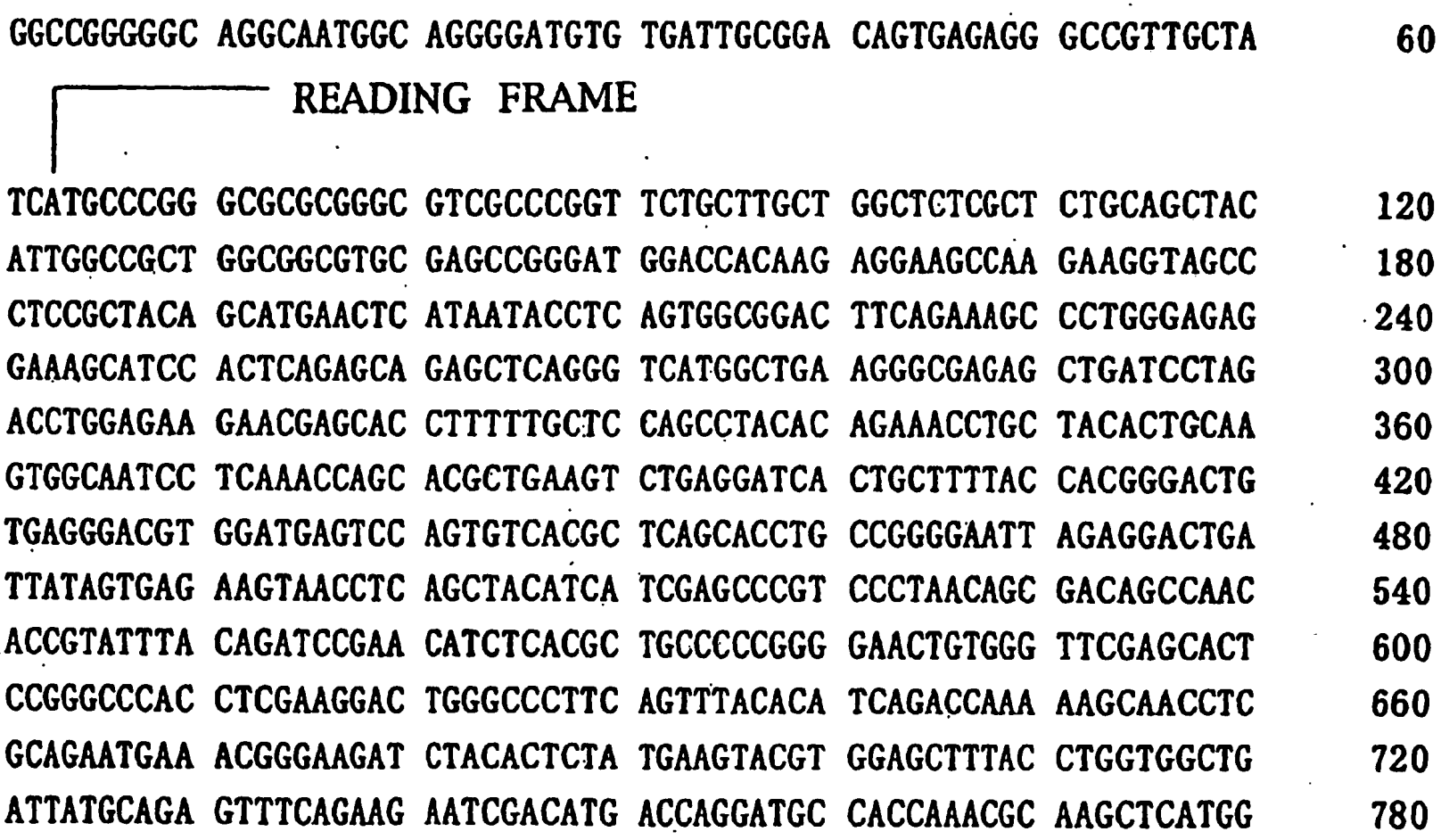
GGCCGGGGGC AGGCAATGGC AGGGGATGTG TGATTGCGGA CAGTGAGAGG GCCGTTGCTA 60
READING FRAME
TCATGCCCGG GCGCGCGGGC GTCGCCCGGT TCTGCTTGCT GGCTCTCGCT CTGCAGCTAC 120
ATTGGCCGCT GGCGGCGTGC GAGCCGGGAT GGACCACAAG AGGAAGCCAA GAAGGTAGCC 180
CTCCGCTACA GCATGAACTC ATAATACCTC AGTGGCGGAC TTCAGAAAGC CCTGGGAGAG 240
GAAAGCATCC ACTCAGAGCA GAGCTCAGGG TCATGGCTGA AGGGCGAGAG CTGATCCTAG 300
ACCTGGAGAA GAACGAGCAC CTTTTTGCTC CAGCCTACAC AGAAACCTGC TACACTGCAA 360
GTGGCAATCC TCAAACCAGC ACGCTGAAGT CTGAGGATCA CTGCTTTTAC CACGGGACTG 420
TGAGGGACGT GGATGAGTCC AGTGTCACGC TCAGCACCTG CCGGGGAATT AGAGGACTGA 480
TTATAGTGAG AAGTAACCTC AGCTACATCA TCGAGCCCGT CCCTAACAGC GACAGCCAAC 540
ACCGTATTTA CAGATCCGAA CATCTCACGC TGCCCCCGGG GAACTGTGGG TTCGAGCACT 600
CCGGGCCCAC CTCGAAGGAC TGGGCCCTTC AGTTTACACA TCAGACCAAA AAGCAACCTC 660
GCAGAATGAA ACGGGAAGAT CTACACTCTA TGAAGTACGT GGAGCTTTAC CTGGTGGCTG 720
ATTATGCAGA GTTTCAGAAG AATCGACATG ACCAGGATGC CACCAAACGC AAGCTCATGG 780

FIG. 6b

```
AGATTGCCAA CTATGTTGAT AAGTTTTACC GCTCCCTGAA CATCCGAATT GCACTTGTCG     840
GCTTGGAGGT GTGGACGCAT GGGGATAAGT GTGAAGTTTC AGAGAATCCC TACTCTACCC     900
TCTGGTCCTT TCTTAGTTGG AGGCGCAAGC TGCTTGCTCA GAAGAGCCAT GACAATGCTC     960
AGCTAATCAC GGGCAGGTCC TTCCAAGGCA CCACCATTGG CCTGGCCCCC CTCATGGCCA    1020
TGTGCTCCGT GTACCAGTCT GGAGGAGTTA GCATGGACCA CTCCGAGAAT GCCATTGGTG    1080
TAGCCTCCAC TGTGGCCCAT GAGATTGGCC ACAACTTTGG CATGAGCCAT GATTCTGCAC    1140
ACTGCTGTTC TGCCAGTGCA GCCGATGGCG GCTGCATCAT GGCCGCCGCC ACCGGGCACC    1200
CTTTCCCCAA AGTGTTCAGT TGGTGTAACA GGAAGGAGCT GGACAGGTAT CTGCAGACAG    1260
GAGGAGGGAT GTGTCTCTCC AACATGCCGG ACACTAGGAC GCTGTATGGA GGCCGGAGGT    1320
GTGGCAACGG GTACCTGGAA GACGGTGAAG AATGTGACTG TGGAGAAGAG GAGGAATGTA    1380
AGAACCCTTG CTGCAATGCC TCCAACTGCA CTCTGAAGGA AGGGGCAGAG TGTGCCCATG    1440
GTTCCTGCTG CCACCAGTGC AAGCTGGTGG CTCCTGGAAC CCAGTGTCGG GAGCAGGTTC    1500
GGCAATGTGA CCTCCCCGAG TTCTGCACCG GCAAGTCTCC CCACTGCCCC ACCAACTATT    1560
ATCAGATGGA TGGCACCCCC TGCGAGGGTG GCCAGGCCTA CTGCTACAAC GGCATGTGCC    1620
TCACTTACCA GGAACAGTGC CAGCAGCTGT GGGGACCTGG AGCCCGGCCT GCCCTCGATC    1680
```

FIG. 6c

```
TTTGCTTTGA GAGGGTGAAT GCTGCTGGTG ACACCTATGG AAACTGTGGC AAGGGCTTGA   1740
ATGGCCAATA CAGGAAGTGC AGTCCCAGGG ATGCCAAGTG TGGSAAGATT CAGTGCCAGA   1800
GCACCCAGGC CCGGCCCCTG GAATCCAACG CAGTATCTAT TGACACCACC ATCACCTTGA   1860
ACGGGAGGCG GATCCACTGT CGGGGCACCC ACGTCTACCG GGGTCCTGAG GAGGAGGAAG   1920
GGGAAGGTGA CATGCTGGAC CCAGGGCTGG TGATGACTGG AACCAAGTGT GGCCACAACC   1980
ATATTTGCTT CGAGGGGCAG TGCAGGAACA CCTCCTTCTT TGAGACGGAA GGCTGTGGGA   2040
AAAAGTGCAA TGGCCACGGG GTCTGCAACA ACAACAAGAA CTGTCATTGC TTCCCTGGCT   2100
GGTCTCCACC TTTCTGTAAC ACCCCGGGAG ATGGTGGCAG CGTCGACAGT GGTCCTTTGC   2160
CCCCTAAGAG TGTGGGTCCC GTGATCGCTG GGGTGTTTTC AGCTCTCTTC GTGTTGGCAG   2220
TTCTGGTGCT ACTGTGTCAC TGCTACAGAC AGAGCCACAA ACTGGGCAAA CCCTCGGCTC   2280
TCCCTTTCAA GCTGCGGCAT CAGTTCAGTT GTCCCTTCAG GGTATCTCAG AGTGGTGGAA   2340
CTGGCCATGC CAACCCAACT TTCAAGTTGC AGACCCCCCA GGGCAAGCGA AAGGTGACTA   2400
ACACCCCTGA ATCCCTCCGG AAGCCGTCCC ACCCCCCTCT CCGGCCCCCT CCAGACTACC   2460
TGCGCGTTGA ATCGCCACCT GCACCATTGT CGGCACATCT GAACAGGGCT GCTGGGAGCT   2520
CCCCAGAAGC TGGGGCTCGA ATAGAAAGAA AGGAGTCAGC CAGGAGGCCT CCCCCAAGCC   2580
```

FIG. 6d

```
GACCCATGCC CCCTGCACCT AACTGCCTAC TGTCCCAGGA CTTCTCCAGG CCTCGACCAC   2640
CTCAGAAGGC ACTCCCAGCC AATCCGGTGC CAGGCCAAAG GACCGGTCCC AGGTCAGGAG   2700
GCACCTCCCT GCTTCAGCCC CCTACTTCTG GTCCTCAGCC CCCCAGGCCT CCAGCAGTGC   2760
```

READING FRAME ——

```
CTGTTCCAAA GCTACCCGAG TACCGATCAC AGAGGGTTGG AGCAATAATT AGCTCCAAGA   2820
```

```
TCTAGAAGTG TCGAGAAGTT TCTTGTTCCG ATGGAAGACT CCGGATGCCA TGGAAGGTCC   2880
AGAAGAAAGA CGCCTTCTCA CCCATCCTGA AGCTTTGGCA GCCTTCTGGA ACGTCCCTCA   2940
TCCCCAGAAT CTCCCTTCTT ACCCGAGTGC CTCCTGCTTC CTCCGAGGCC CAGGGGGACT   3000
CATATCCAAT GGCTCCTAAG TGTTTGTCCT GTGCAATATA CAGCCCAGGG AGGGAAGGGA   3060
AGCACGGCGA GGAGGGTGGG AAAGGTTCTC CCTCAGCCCA CTAGCCAAGA GCTACCAGCG   3120
```

FIG. 6e

```
ATGCTCAGGG AAGGCTTGAG CTGGGGTCCT CCTCTGCGGA GCTTGGAGAA GGTACCCATC    3180
CTGGTCCTAT GCTGGCAGGA ACACACGCGA GTGTCACTGA TTGGCCTCCT TCTGGGATCC    3240
CAGGCTGCTG AGGAAGCTAC TGCTACATCC CTACCCCAAG GGGCTTGGTC AAGGTGCCTG    3300
TYCCTGGCTC TCTGGCTGCA TGTAATAAGC CATGCTCCCC TCCCCTGCCT TTCTTCACAT    3360
TCCCACTCCC ATATTTACAC GGGTCACTCT GACTCAGACA GGTACTATTT GTAAGTAGCA    3420
TAGACAGCAG GGGGGTGGGG TGGTCAACCT GTGTCCCCTC TGAGCCGTTA TGCCAAAGGT    3480
CACTAAGGAC ATTTAGAATC CCCATCCATC CATCCATCCA TCCATCCATC CATCCATTCA    3540
TCCATCCCCA GTGTTCCATG TGTCACCTTC TCCTTTTCCA GCATCCCTAT CCTATGGTGC    3600
TTTGGTGGTG AACTATGGCA GTCCTGACTT GCTGATGACC ATATGCTGGT GACCTACAAA    3660
TCGGGATCCT GCCATATGGG GTCGCCACTG GACTTTCTGC ACTGGTTCTC AAGAGCGTTG    3720
AGCCGAGTGG GCGTGTATGT TTGTGTGTGT GTGTGTGTGT GTGTGTGTGT GTGTGTGTGT    3780
GTGTGTGTGT GTGTGTGTGT GTGAAAGAGA CAGAGGCAAT GAGAGAGACA GACATGCAGG    3840
CAGGCCGACA GCTCTGCATG TACTTGTGTT TTACGGCCTC AAGCAGTATA AGGGACCTCC    3900
TCCTTATTTC TGACTCATAT CTAAGTAAGG TTCCCCAGGA CMAGCCACAG CTGTACTGAG    3960
GGGGGCTGAC ATGTTTGGCA TCCTGGCTAT AGTATTGTAT ACACAGGGCC ACCAGCCCCG    4020
```


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FIG. 6f

```
CCCTAGTGGT CAGCTCTGAG GGGGGACTGG TGACTCTGAA CAGATCGATG TCAACAGCCA  4080
TGGTGAACCA GATCTGGGCA GGGTTCCCCA AACTCTATTC AACCAGAGTT TTATCACGCA  4140
NCTCATCGGG TCTCTCCTGG TTGCTGCCCC GAGGTGATCG TCATGGAAAA TGCTGAGAAG  4200
GTGGGAATGG GATGGGGTGG ACCTTCTCTT GCTTGGTGCT CCGCTATTTG GAACAGTTCT  4260
TACACATTTG CTGGGCCTGG CCTCTGAGAG GCCATCTTCC ACCCCCAGAA AGGTGCTAAT  4320
GGCACTGCAG AGGGCTCTCT AGGGGCCTCC CCGCCCCAAC AGCAAGCAGT TGTTAGCTCT  4380
TGGAACCCTC CAGAGGAAGA GGCAAGCGTT TGACTTCCCC TTTACCACCT GAGGCCTCCT  4440
TATATCTCTT CCCAGAGTAA GCTTTGGGAT TGTAGACATG TGGGAGCTAT GACAGACGTG  4500
GCCTGGGGTA GAAAGATCTC AGGAAAGCAC CTTTCTCCTT TTCAGGGTGA CCGTGCTCTT  4560
CACACTCTCT GAGGCCTCAG TCCATGTCCT ATATCAGTTT CTCTTTTGTG TGCTTTACCA  4620
AGTGGCCGGT GACTACAGGC CACCCCGATT CTCACCACAA AGTTAGAAAC CCTCCACTTT  4680
CTGTCCCTTG AACCATATCA GAAAAAGACC CATTTCCTTG CTCTTTGGTA ATCACTTCTG  4740
TTTTTTCTTC TTCATTACTG TGCTACCACC TCCATCCCAT GACATTATTC TGTGANGTGT  4800
AAGAGGACGG TGTTTTNTTA NTCTTGGGAG ANATGTCGGC AGCTGCTCTA CACACAACTT  4860
CACTCAAGGC TTTGTCTCCA GAGGCCAGCT AGGCTGTCAC AGGCAGGAAT CCCTTCCCAT  4920
```


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FIG. 6g

```
CTGCTTTGTG AAGGGTCCCA TACAGGTGTA TCTAGACTTC AAGGACAGGG TTTGTCTCAC   4980
AGGATTGTCA CTTAGGAGAT GAAAGAATAT TACCACATGA GGAGGAGGGG CAGTTGCAAC   5040
AGAACACTTT GGTCTTCCTA CACCAAGTCT GTGAGGGCAT CCAAGACTGA ATGAAAGCGC   5100
TTTTCTTATG CATACAATGT GAGCAAGAAC AAGAACTGTT TAAGGCACCT CTGTTCCCAG   5160
CCACTGAAGA GAGACGTCAG AAGATGTTAG AATAGGTCAA AACCAAGGCT CTGGTGGACT   5220
GAGGGAAGGT TTGTAGCTGC GTTTAGTGGT ATACATCTTT AGTCCCAGCA TAGGCAGGTG   5280
AATCTCGAGT TTGAAGCTAG CCTGGTCTAA AAAGGAAGTT CCAAGACTGC CAGGGCCACA   5340
CAGAGGAAAA AAAAAAACCC TCTAGAAAAA CAAAAATGAA GACAGGTTCT CATGTATCGT   5400
AGATTGGCCT TTAAGTCACT TTACCAAGGA TGATCTTTGA ACTCCTGAGT ACAGACTGCG   5460
GGTGTGTGCT ACCATGCTTT ATGTGGCCCT GGGTTCAAAC ACAGCCCTTC ATATGTATAT   5520
AGCCAAACAC TCTACAACTG AGCTACATCC TCCAGCCTAG GCTGTAAATG TTTTTTGGAG   5580
CTAGATTAGC TGCCTGCCAA CCTTAGAACT GCAAAGCCAT TCCTGACCTG TAAACCTCAG   5640
CTCTCCATCT CTATAAGAGG TATAGCCTGG GCTAATACCG TCCAAGTTAC AACTCCTTGC   5700
TTGCTTTCTG TTCCTTCTAG CCTTGGTGAC TTCCACCAGG AAGAGAATAC CCCCTCTCTA   5760
CCCCTGCTCC AAGACACTGT AGATGCTAGT GTCGGAGTGT TCTCTGTAAC GCGACAGTTC   5820
```

FIG. 6h

```
CTTCTGTTGC AATAGCCCCC CTGCAACACT GCAATAATCC TTCAGTGTCT CCCCTGGGCT    5880
CAATTCACTT CCTTATTTGA CAAAGTGGAG GTGAGACTTG TATTCTTAAA ATTGGAGGCT    5940
AGTTATTTTG TCAAATGCAT GTAATGAACA GACCCGAAGG AATCCTCCAC ACACAAGCCA    6000
GGGAACACCA ACTGGAAAGG TACCCCGTCC CAGGGAAGCC TGCTAGGGAG AGGTTCTGTA    6060
GAATCCGAGC CTAGCACCCC AAAGTCATGC ACCCAGTATC CTCTTGTATG ACTGTATATG    6120
TCTATGTCTG GGATCCAGGG CAAATGTGAA TTTCCTTTTG ATTTGGGAGA TTGTTCACAG    6180
GAAGTAGTCC TCCCCTCTCA TGTCCTCCTA TTGATTGTTT ACAATATTTG TACATCTATG    6240
CAAAATACTT GAATGGGCCA TGGTGCCTTG TTTTTTGTTG TTGTTGTTAT TTTTTTCTCC    6300
TTGTTTGTAT TTAATTAAAA CAAATTGTCA TGAGGAAAAA AAAAAAAAAA AA             6352
```

FIG. 7a

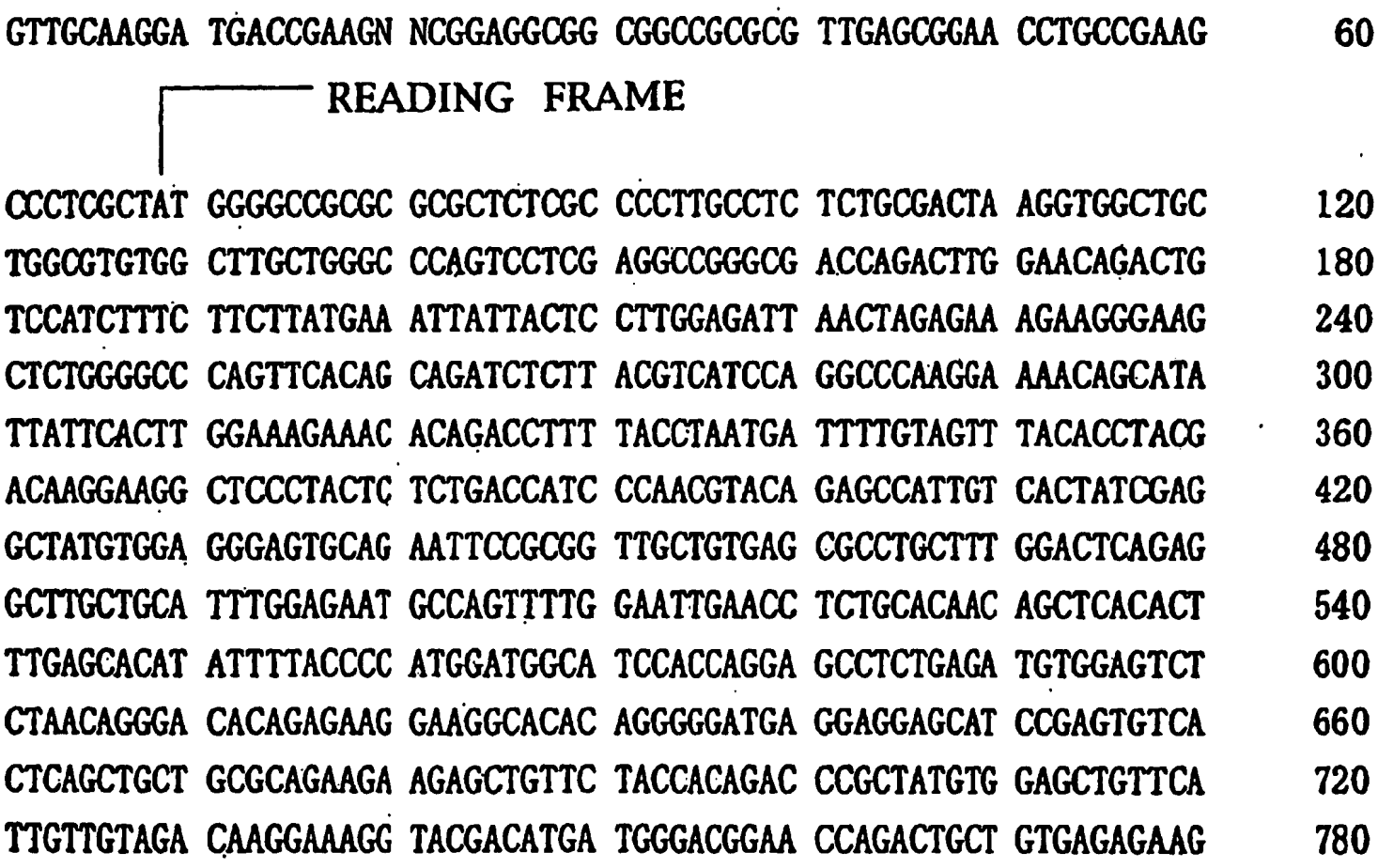
GTTGCAAGGA TGACCGAAGN NCGGAGGCGG CGGCCGCGCG TTGAGCGGAA CCTGCCGAAG 60
READING FRAME
CCCTCGCTAT GGGGCCGCGC GCGCTCTCGC CCCTTGCCTC TCTGCGACTA AGGTGGCTGC 120
TGGCGTGTGG CTTGCTGGGC CCAGTCCTCG AGGCCGGGCG ACCAGACTTG GAACAGACTG 180
TCCATCTTTC TTCTTATGAA ATTATTACTC CTTGGAGATT AACTAGAGAA AGAAGGGAAG 240
CTCTGGGGCC CAGTTCACAG CAGATCTCTT ACGTCATCCA GGCCCAAGGA AAACAGCATA 300
TTATTCACTT GGAAAGAAAC ACAGACCTTT TACCTAATGA TTTTGTAGTT TACACCTACG 360
ACAAGGAAGG CTCCCTACTC TCTGACCATC CCAACGTACA GAGCCATTGT CACTATCGAG 420
GCTATGTGGA GGGAGTGCAG AATTCCGCGG TTGCTGTGAG CGCCTGCTTT GGACTCAGAG 480
GCTTGCTGCA TTTGGAGAAT GCCAGTTTTG GAATTGAACC TCTGCACAAC AGCTCACACT 540
TTGAGCACAT ATTTTACCCC ATGGATGGCA TCCACCAGGA GCCTCTGAGA TGTGGAGTCT 600
CTAACAGGGA CACAGAGAAG GAAGGCACAC AGGGGGATGA GGAGGAGCAT CCGAGTGTCA 660
CTCAGCTGCT GCGCAGAAGA AGAGCTGTTC TACCACAGAC CCGCTATGTG GAGCTGTTCA 720
TTGTTGTAGA CAAGGAAAGG TACGACATGA TGGGACGGAA CCAGACTGCT GTGAGAGAAG 780

FIG. 7b

```
AGATGATTCG CTTAGCAAAC TACCTGGATA GCATGTACAT CATGTTAAAC ATTCGAATTG     840
TGCTGGTTGG ACTAGAAATT TGGACAGACA GAAATCCTAT CAATATAATT GGAGGAGCTG     900
GAGATGTGCT GGGCAACTTT GTTCAGTGGC GGGAAAAGTT CCTTATAACT CGTCGGAGAC     960
ACGACAGTGC ACAGTTGGTT TTGAAGAAAG GCTTTGGTGG AACTGCAGGA ATGGCGTTTG    1020
TAGGAACAGT ATGTTCAAGG AGCCACGCAG GTGGGATCAA TGTGTTTGGG CAAATCACTG    1080
TGGAGACATT TGCATCCATT GTTGCTCATG AATTGGGGCA TAACCTTGGA ATGAATCATG    1140
ATGATGGGAG AGAGTGTTTC TGTGGAGCAA AGAGCTGTAT CATGAATTCA GGAGCATCCG    1200
GGTCCAGAAA CTTTAGCAGT TGCAGTGCGG AGGACTTTGA GAAGTTAACG TTGAATAAGG    1260
GAGGAAGCTG CCTGCTTAAC ATCCCGAAGC CTGACGAAGC CTACAGCGCG CCCTCCTGTG    1320
GTAATAAGCT GGTGGACCCT GGAGAGGAGT GTGACTGCGG CACAGCGAAG GAGTGTGAGG    1380
TGGACCCATG CTGTGAAGGA AGCACTTGTA AGCTCAAGTC ATTTGCTGAG TGTGCATATG    1440
GCGACTGTTG TAAAGATTGC CAGTTCCTTC CAGGAGGCTC CATGTGCAGA GGGAAGACCA    1500
GTGAGTGTGA TGTTCCTGAG TACTGCAACG GTTCCTCTCA GTTCTGCCCG CCAGATGTCT    1560
TCATTCAGAA TGGATATCCT TGCCAGAACA GCAAAGCCTA CTGCTACAAT GGCATGTGCC    1620
AATATTATGA CGCGCAGTGT CAGGTCATCT TTGGTTCAAA GGCTAAGGCT GCCCCAAGAG    1680
```


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FIG. 7c

```
ATTGCTTCAT TGAAGTCAAT TCTAAAGGTG ACAGATTTGG CAACTGTGGT TTCTCCGGCA  1740
GTGAGTACAA GAAGTGTGCC ACTGGGAACG CGCTGTGTGG AAAGCTTCAA TGCGAGAATG  1800
TACAGGACAT GCCGGTGTTT GGAATAGTAC CAGCTATCAT TCAGACACCC AGTCGAGGCA  1860
CCAAATGCTG GGGTGTGGAT TTCCAGCTTG GTTCCGACGT TCCAGACCCA GGGATGGTGA  1920
ATGAAGGCAC CAAATGTGAT GCTGGCAAGA TTTGCAGGAA TTTTCAGTGT GTAAATGCTT  1980
CTGTCCTGAA TTATGACTGT GACATTCAGG GAAAATGTCA TGGCCATGGG GTATGTAACA  2040
GCAATAAGAA TTGTCACTGT GAAGATGGCT GGGCTCCCCC ACACTGTGAC ACCAAAGGAT  2100
ATGGAGGAAG CGTGGACAGC GGGCCGACGT ATAATGCAAA GAGCACAGCA CTGAGGGACG  2160
GGCTTCTGGT CTTCTTCTTC CTAATCGTCC CCCTTGTTGC GGCTGCCATT TTCCTCTTTA  2220
TCAAGAGAGA TGAACTACGG AAAACCTTCA GGAAGAAGAG ATCACAAATG TCAGATGGCA  2280
GAAATCAAGC AAACGTCTCT AGACAGCCAG GAGATCCTAG TATCTCCAGA CCACCAGGGG  2340
GCCCAAATGT CTCCAGACCA CCAGGGGGCC CAGGTGTCTC CAGACCACCA GGGGGCCCAG  2400
GTGTCTCCAG ACCACCAGGG GGCCCAGGTG TCTCCAGACC GCCACCTGGG CATGGAAACA  2460
GATTCCCAGT ACCAACCTAC GCCGCCAAGC AGCCTGCGCA GTTCCCGTCA AGGCCACCTC  2520
CACCACAACC GAAAATATCT TCTCAGGGAA ACTTGATTCC GGCTCGGCCC GCTCCTGCAC  2580
```


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FIG. 7d

READING FRAME

```
CTCCTTTATA TAGCTCCCTC ACCTGATAGT AGAATATTAG AATCTTATTT TTTAAATGTC   2640
TTCAGGGAAC TGAGCAAATG TTTGTTGTTT TTTTTTTCCT GATGTTTTCT TGAAAAGCCT   2700
TTCTCTTCCA ACCATGAATG AACACAAACC ACCACAAAAC AAGCTTTATT AACACAGGAG   2760
CCTAGTGGGG ATTGCGAAAC ACAGGAATGT GCAGGCGCTC CGGGGGGTGT AAAGTGAACG   2820
TTTCCATCGT TAGAATGTTT TCTCTGGCCA TTTGTGGATT TAATGCACTT GACGTGGATT   2880
AAGTTATTCT GAGCATGTTA CTGTAATGAT TCTCAAATTA ACTGTATTAG TGTAAGCTTT   2940
GTCACTATGC GCTAAACGTA ATCCTGACTT TTTGACCCCA GTTACCATTA ATAGTTTCTG   3000
GTTGACCATT TGAACATGTA TTAACTTAGG AAGACTAATT GCCAATAACG TCTGCATTTT   3060
CATCTTGCAT GGATTAACAG CCATTTATAT GGACTTATGT CTCTTAATGC ACAAAGAAGC   3120
AGATATCTCG AAGGAGCTTA CACAAGAACC ACAATTACTA GATCATGATA TACTTGGAAA   3180
GTGTGAAATA TGGTGTGTAC TCAGTTATTG GCTTCCATTT TTWATGATCT TTCAACTATA   3240
ACAATTATGA TAGAAATCGA TTTAACACAA TCAGTTATGG GCTTCCATTT TCAAATATCT   3300
TTTCAACTGT AATGACTATG ACAGGAACTG ATTCAACTCT CAATTTTCTT TATGCATCAT   3360
```

FIG. 7e

```
GGTAAAGCAT TGCAGCAGTG TTGTTTTGTT TGAAGTGCAC ACTCTATGGT ACGAGGTGTT    3420
TAGTATACCC AAGCAGATAG GTGTCGATCG AACAGGAGCA GGGAGAATAC TTCCAACAGT    3480
TGAGGTGTTA CCAAACCACT TGAGAATTCA TGAGCACTTT AACTCTAAAC TCTGAATTTC    3540
AAAGCTTGAT GTGAAGTCCT CTAGAATGTT TACATTTACT AAGGTGTGCT GGGTCCTGTC    3600
TCTTTTGACT AATATTTTCG TAAACATTAG GCTGGAGAAA GGAAGGAAGC AGTGGTTTCC    3660
TTAGATAACT ACAGAATTAT ACTGGTCTCT GGGATTACTC TCTCAGCTGT ATTAAAATGA    3720
ATTTGTACTT TGAAAGGAAT GATATTGACA CTAAAATTTT AAACATTTAA ATTTTTTCAT    3780
AATCTTTCAT AAAGAAGTTT AATAATAGGT ATATTAACTG AATTTCATTA GTTTTTTAAA    3840
ATAATATTGT TTGTGTATAT ATACATATTA AAATAAAAAC ATTTACAACA AATAAAATAC    3900
TTGAAATTCT AAAAAAAAAA AAAAAAAAAA A                                   3931
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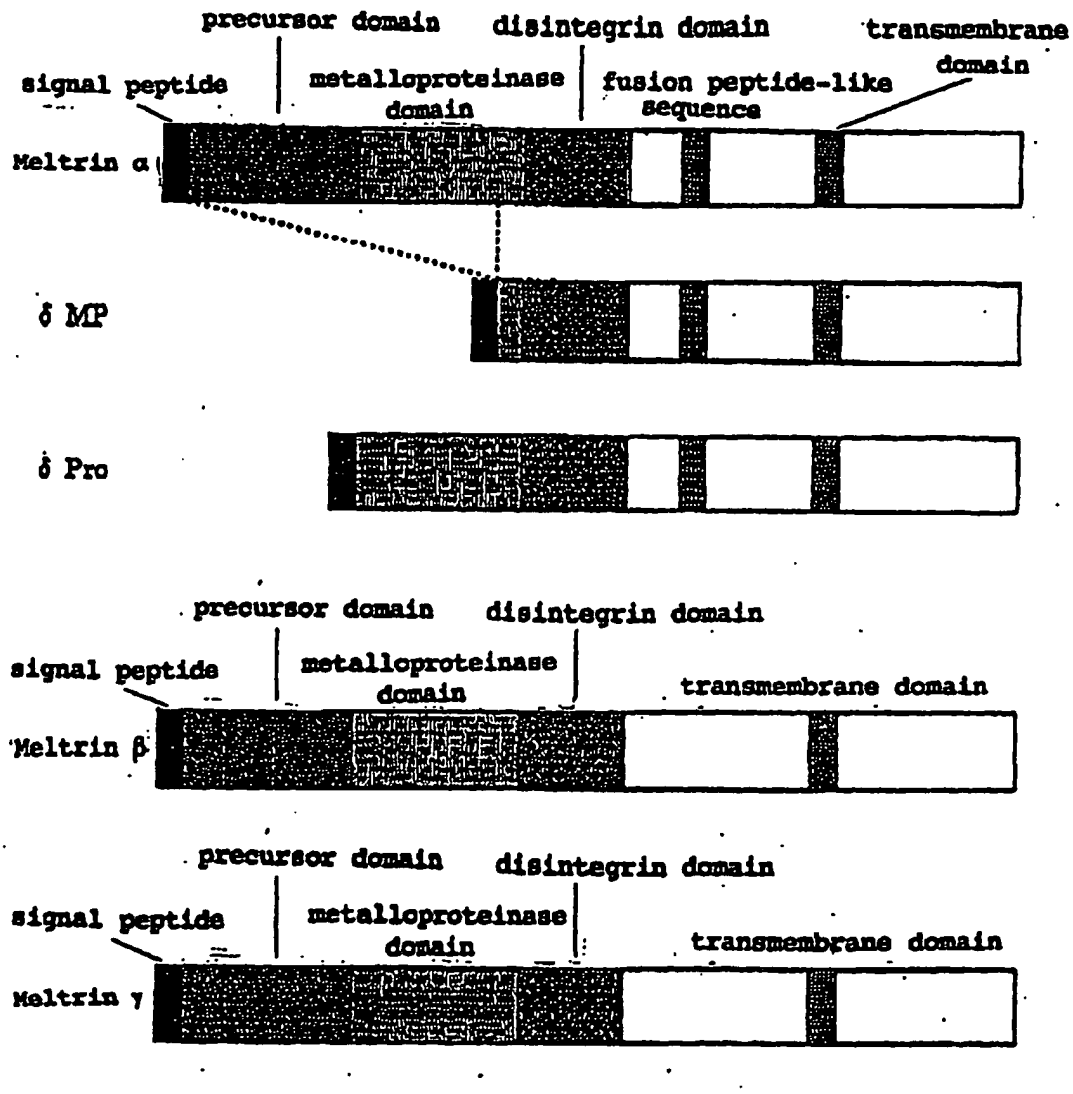
FIG. 8


precursor domain
disintegrin domain
transmembrane domain
signal peptide
metalloproteinase domain
fusion peptide-like sequence
Meltrin α
δ MP
δ Pro
precursor domain
disintegrin domain
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transmembrane domain
Meltrin γ

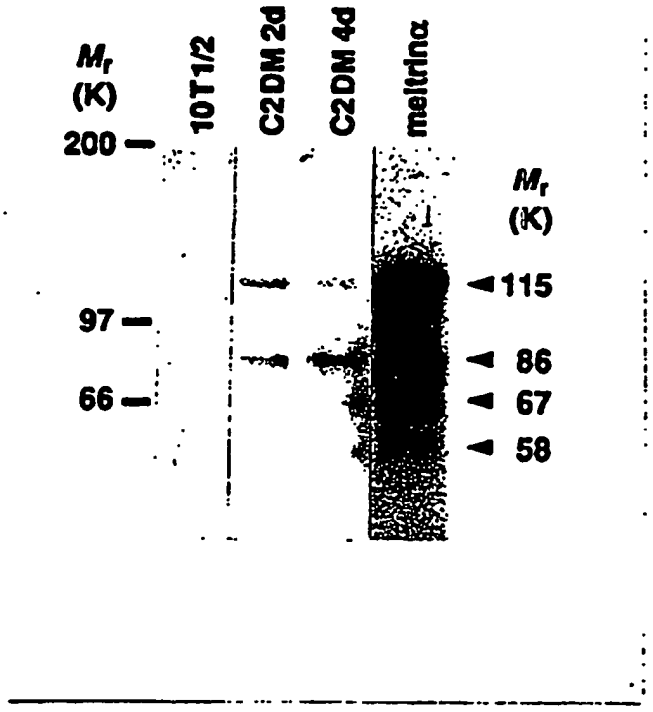

FIG. 9

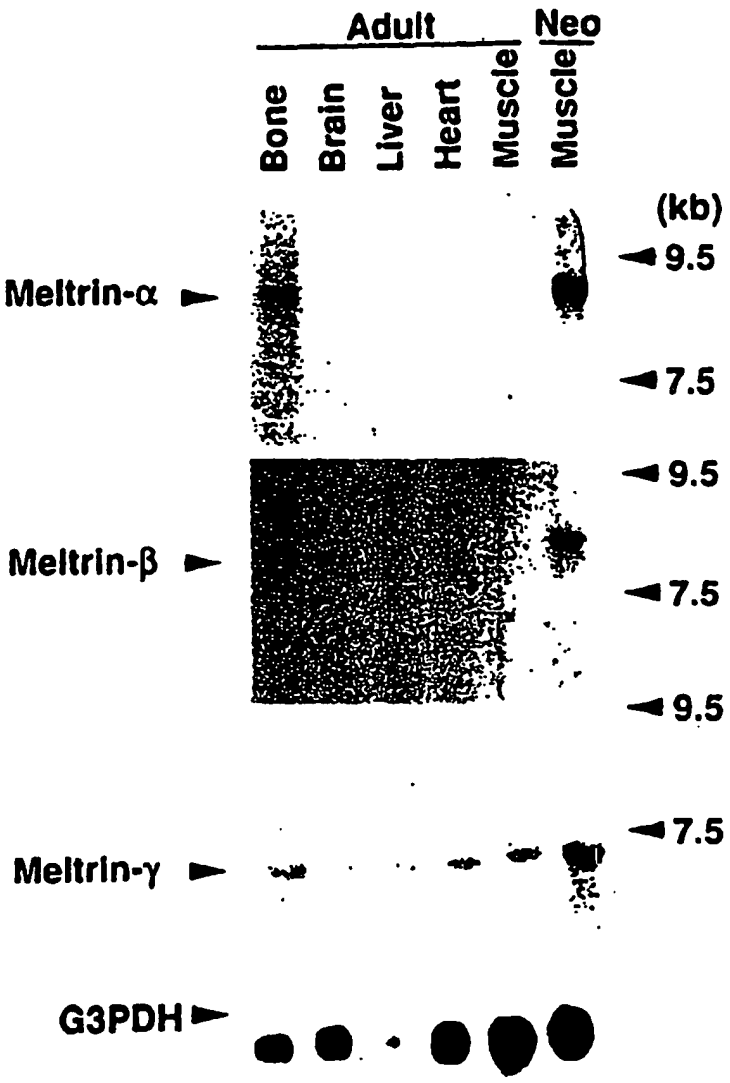
Adult
Neo
Bone
Brain
Liver
Heart
Muscle
Muscle
(kb)
Meltrin-α
9.5
7.5
Meltrin-β
9.5
7.5
9.5
Meltrin-γ
7.5
G3PDH

FIG. 10

FIG. 11a

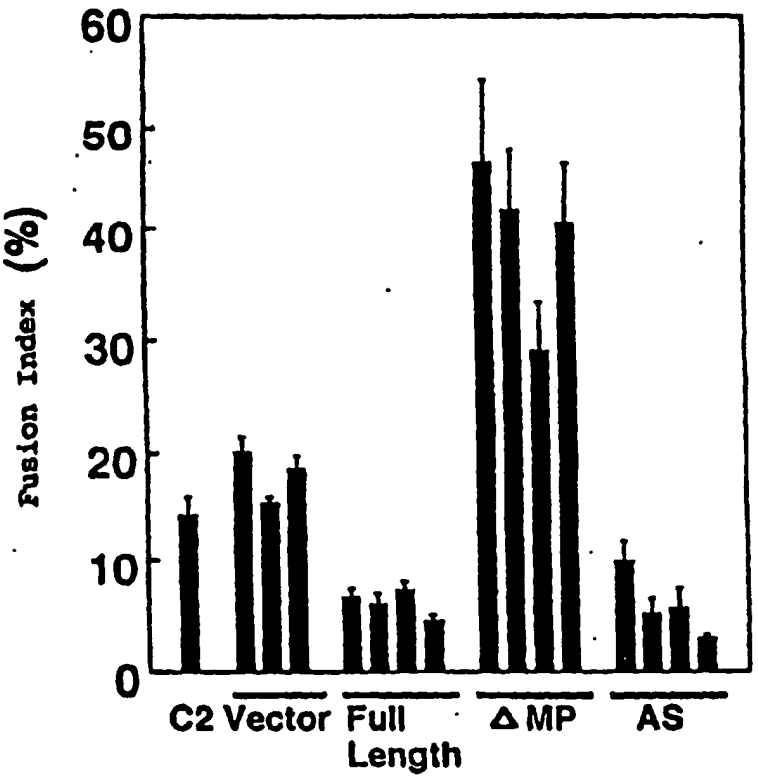

FIG. 11b

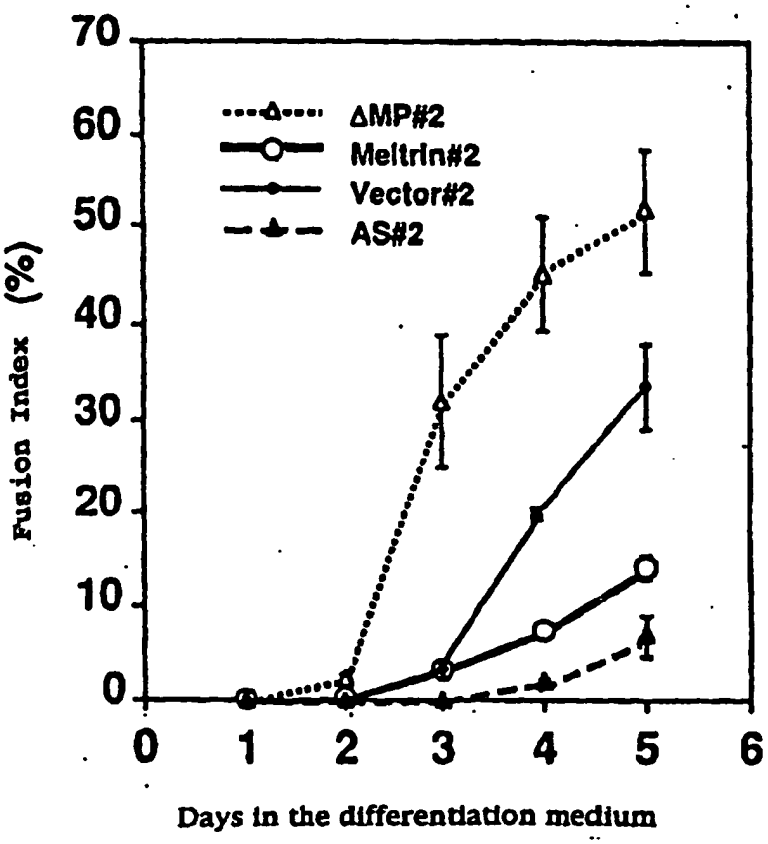
70
60
50
40
30
20
10
0
Fusion Index (%)
ΔMP#2
Meltrin#2
Vector#2
AS#2
0
1
2
3
4
5
6
Days in the differentiation medium

FIG. 12a

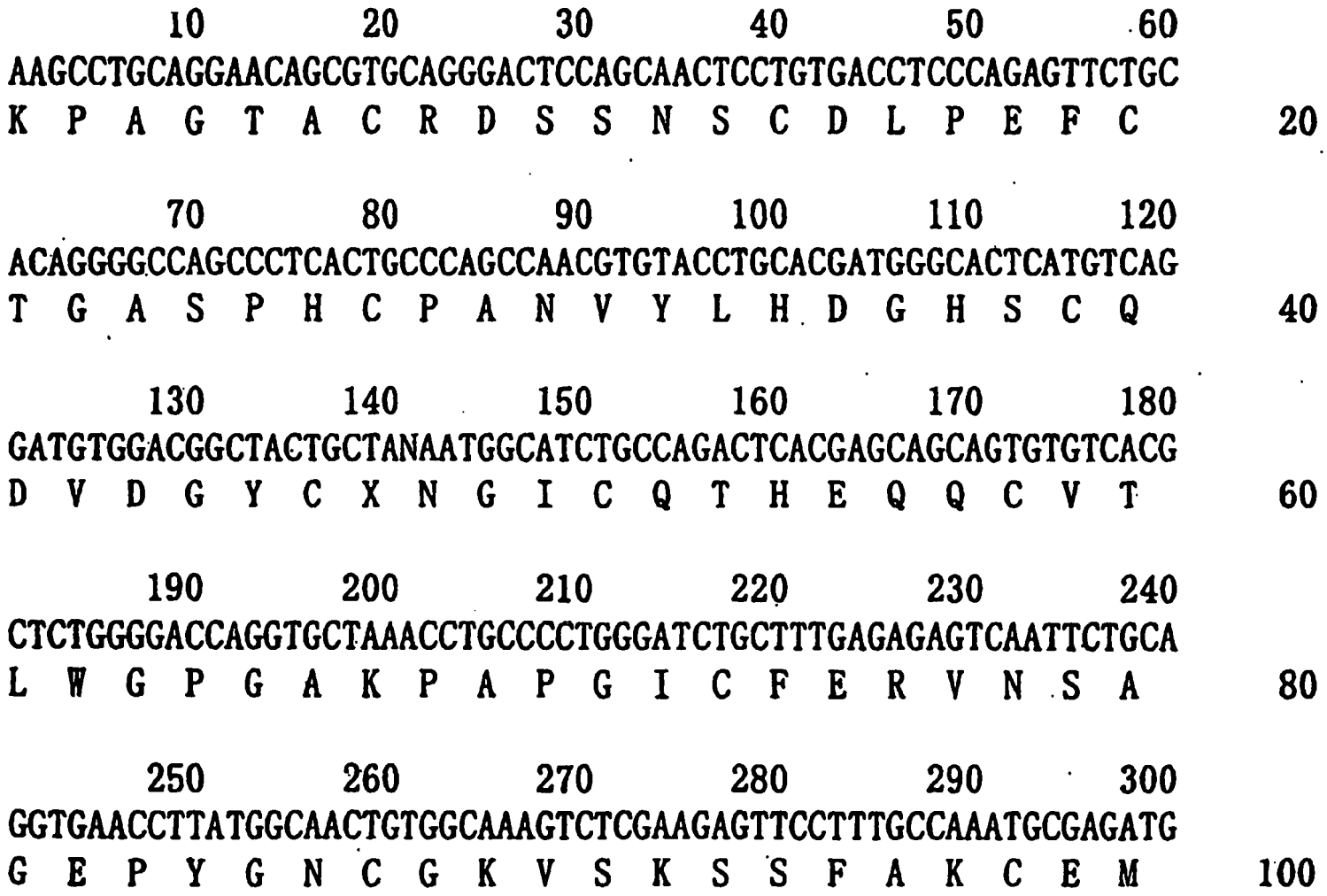

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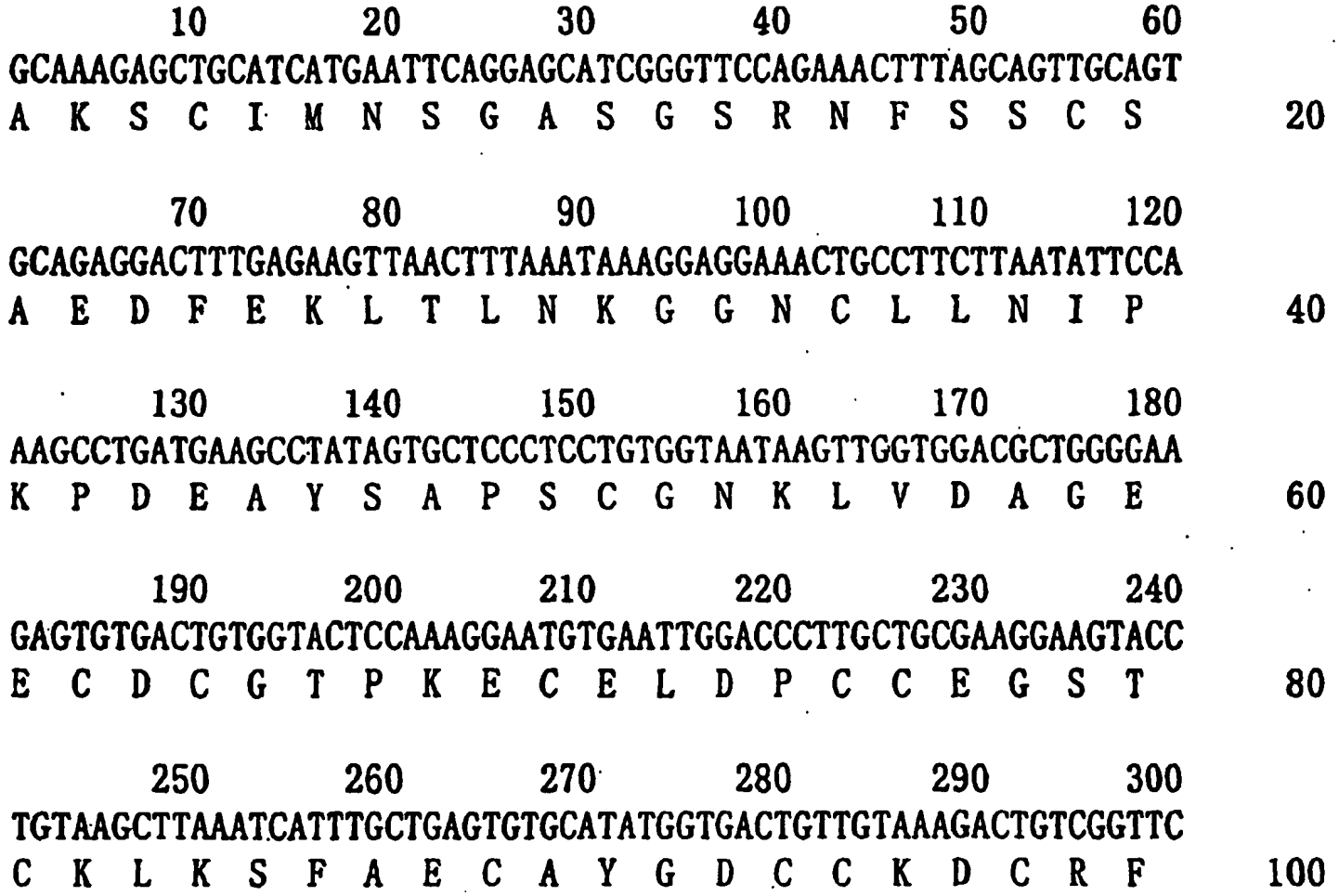
FIG. 12b

310 320

AGAGATGCTAAATGCGGCAAG

R D A K C G K 107

FIG. 13a



150

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FIG. 13b

```
        310        320        330        340        350        360
CTTCCAGGAGGTACTTTATGCCGAGGAAAAACCAGTGAGTGTGATGTTCCAGAGTACTGC
L  P  G  G  T  L  C  R  G  K  T  S  E  C  D  V  P  E  Y  C      120

        370        380        390        400        410        420
AATGGTTCTTCTCAGTTCTGTCAGCCAGATGTTTTTATTCAGAATGGATATCCTTGCCAG
N  G  S  S  Q  F  C  Q  P  D  V  F  I  Q  N  G  Y  P  C  Q      140

        430        440        450        460        470        480
AATAACAAAGCCTATTGCTACAACGGCATGTGCCAGTATTATGATGCTCAATGTCAAGTC
N  N  K  A  Y  C  Y  N  G  M  C  Q  Y  Y  D  A  Q  C  Q  V      160

        490        500        510        520        530        540
ATCTTTGGCTCAAAAGCCAAGGCTGCCCCCAAAGATTGTTTCATTGAAGTGAATTCTAAA
I  F  G  S  K  A  K  A  A  P  K  D  C  F  I  E  V  N  S  K      180

        550        560        570        580        590        600
GGTGACAGATTTGGCAATTGTGGTTTCTCTGGCAATGAATACAAGAAGTGTGCCACTGGG
G  D  R  F  G  N  C  G  F  S  G  N  E  Y  K  K  C  A  T  G      200
```


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FIG. 13c

```
      610        620        630        640        650        660
AATGCTTTGTGTGGAAAGCTTCAGTGTGAGAATGTACAAGAGATACCTGTATTTGGAATT
N  A  L  C  G  K  L  Q  C  E  N  V  Q  E  I  P  V  F  G  I      220

      670        680        690        700        710        720
GTGCCTGCTATTATTCAAACGCCTAGTCGAGGCACCAAATGTTGGGGTGTGGATTTCCAG
V  P  A  I  I  Q  T  P  S  R  G  T  K  C  W  G  V  D  F  Q      240

      730        740        750        760        770        780
CTAGGATCAGATGTTCCAGATCCTGGGATGGTTAACGAAGGCACAAAATGTGGTGCTGGA
L  G  S  D  V  P  D  P  G  M  V  N  E  G  T  K  C  G  A  G      260

      790        800        810        820        830        840
AAGATCTGTAGAAACTTCCAGTGTGTAGATGCTTCTGTTCTGAATTATGACTGTGATGTT
K  I  C  R  N  F  Q  C  V  D  A  S  V  L  N  Y  D  C  D  V      280

      850        860        870        880        890        900
CAGAAAAAGTGTCATGGACATGGGGTATGTAATAGCAATAAGAATTGTCACTGTGAAAAT
Q  K  K  C  H  G  H  G  V  C  N  S  N  K  N  C  H  C  E  N      300
```


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FIG. 13d

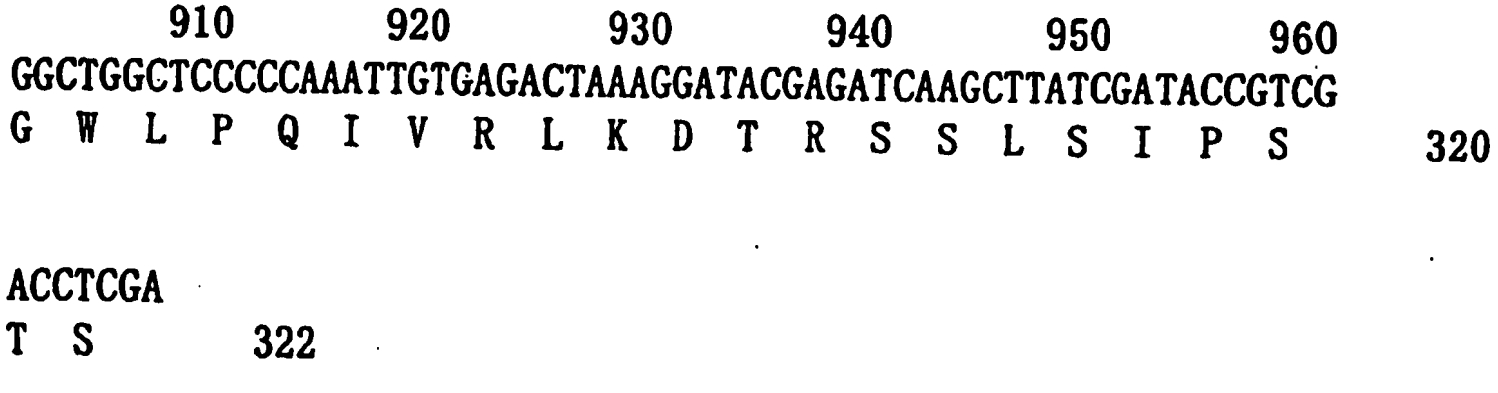
910
920
930
940
950
960
GGCTGGCTCCCCCAAATTGTGAGACTAAAGGATACGAGATCAAGCTTATCGATACCGTCG
G W L P Q I V R L K D T R S S L S I P S
320
ACCTCGA
T S
322

FIG. 14a

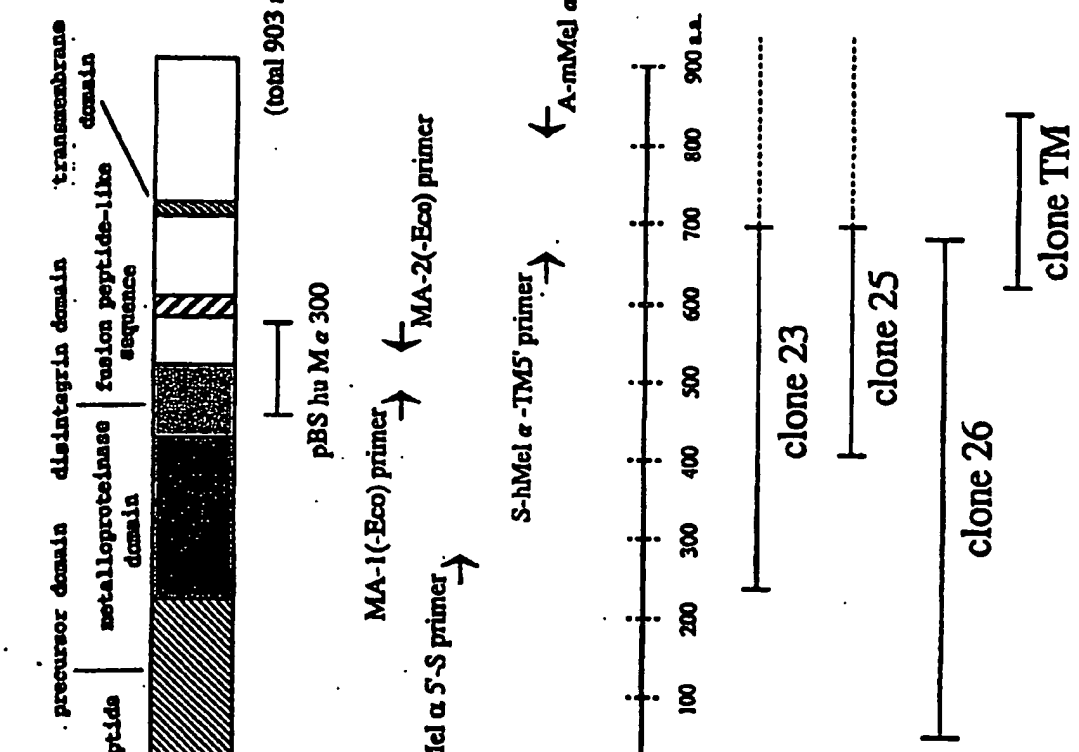
Meltrin - α
signal peptide
precursor domain
metalloproteinase domain
disintegrin domain
fusion peptide-like sequence
transmembrane domain
(total 903 a.a.)
pBS hu M α 300
MA-1(-Eco) primer
MA-2(-Eco) primer
Mel α 5'-S primer
S-hMel α -TM5' primer
A-mMel α -3' primer
0
100
200
300
400
500
600
700
800
900 a.a.
clone 23
clone 25
clone 26
clone TM

FIG. 14b

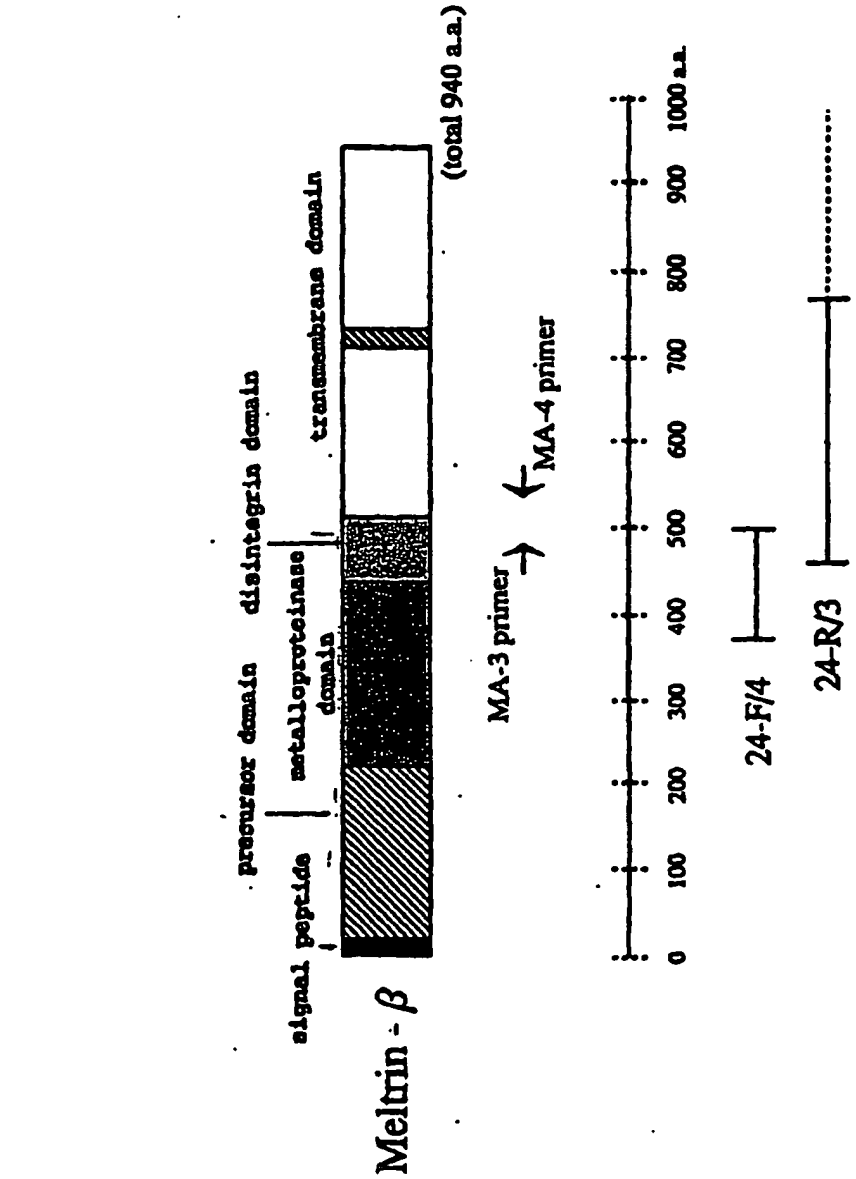
Meltrin - β
signal peptide
precursor domain
metalloproteinase domain
disintegrin domain
transmembrane domain
(total 940 a.a.)
MA-3 primer
MA-4 primer
24-F/4
24-R/3
0
100
200
300
400
500
600
700
800
900
1000 a.a.

FIG. 15a

```
GGGGACCTCTGGATCCCAGTGAAGAGCTTCGACTCCAAGAATCATCCAGAAGTGCTGAAT    60
G  D  L  W  I  P  V  K  S  F  D  S  K  N  H  P  E  V  L  N     20

ATTCGACTACAACGGGAAAGCAAAGAACTGATCATAAATCTGGAAAGAAATGAAGGTCTC   120
I  R  L  Q  R  E  S  K  E  L  I  I  N  L  E  R  N  E  G  L     40

ATTGCCAGCAGTTTCACGGAAACCCACTATCTGCAAGACGGTACTGATGTCTCCCTCGCT   180
I  A  S  S  F  T  E  T  H  Y  L  Q  D  G  T  D  V  S  L  A     60

CGAAATTACACGGGTCACTGTTACTACCATGGACATGTACGGGGATATTCTGATTCAGCA   240
R  N  Y  T  G  H  C  Y  Y  H  G  H  V  R  G  Y  S  D  S  A     80

GTCAGTCTCAGCACGTGTTCTGGTCTCAGGGGACTTATTGGGTTTGAAAATGAAAGCTAT   300
V  S  L  S  T  C  S  G  L  R  G  L  I  G  F  E  N  E  S  Y    100

GTCTTAGAACCAATGAAAAGTGCAACCAACAGATACAAACTCTTCCCAGCGAAGAAGCTG   360
V  L  E  P  M  K  S  A  T  N  R  Y  K  L  F  P  A  K  K  L    120

AAAAGCGTCCGGGGATCATGTGGATCACATCACAACACACCAAACCTCGCTGCAAAGAAT   420
K  S  V  R  G  S  C  G  S  H  H  N  T  P  N  L  A  A  K  N    140
```


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FIG. 15b

```
GTGTTTCCACCACCCTCTCAGACATGGGCAAGAAGGCATAAAAGAGAGACCCTCAAGGCA   480
V  F  P  P  P  S  Q  T  W  A  R  R  H  K  R  E  T  L  K  A      160

ACTAAGTATGTGGAGCTGGTGATCGTGGCAGACAACCGAGAGTTTCAGAGGCAAGGAAAA   540
T  K  Y  V  E  L  V  I  V  A  D  N  R  E  F  Q  R  Q  G  K      180

GATCTGGAAAAAGTTAAGCAGCGATTAATAGAGATTGCTAATCACGTTGACAAGTTTTAC   600
D  L  E  K  V  K  Q  R  L  I  E  I  A  N  H  V  D  K  F  Y      200

AGACCACTGAACATTCGGATCGTGTTGGTAGGCGTGGAAGTGTGGAATGACATGGACAAA   660
R  P  L  N  I  R  I  V  L  V  G  V  E  V  W  N  D  M  D  K      220

TGCTCTGTAAGTCAGGACCCATTCACCAGCCTCCATGAATTTCTGGACTGGAGGAAGATG   720
C  S  V  S  Q  D  P  F  T  S  L  H  E  F  L  D  W  R  K  M      240

AAGCTTCTACCTCGCAAATCCCATGACAATGCGCAGCTTGTCAGTGGGGTTTATTTCCAA   780
K  L  L  P  R  K  S  H  D  N  A  Q  L  V  S  G  V  Y  F  Q      260

GGGACCACCATCGGCATGGCCCCAATCATGAGCATGTGCACGGCAGACCAGTCTGGGGGA   840
G  T  T  I  G  M  A  P  I  M  S  M  C  T  A  D  Q  S  G  G      280
```


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FIG. 15c

```
ATTGTCATGGACCATTCAGACAATCCCCTTGGTGCAGCCGTGACCCTGGCACATGAGCTG   900
I  V  M  D  H  S  D  N  P  L  G  A  A  V  T  L  A  H  E  L     300

GGCCACAATTTCGGGATGAATCATGACACACTGGACAGGGGCTGTAGCTGTCAAATGGCG   960
G  H  N  F  G  M  N  H  D  T  L  D  R  G  C  S  C  Q  M  A     320

GTTGAGAAAGGAGGCTGCATCATGAACGCTTCCACCGGGTACCCATTTCCCATGGTGTTC  1020
V  E  K  G  G  C  I  M  N  A  S  T  G  Y  P  F  P  M  V  F     340

AGCAGTTGCAGCAGGAAGGACTTGGAGACCAGCCTGGAGAAAGGAATGGGGGTGTGCCTG  1080
S  S  C  S  R  K  D  L  E  T  S  L  E  K  G  M  G  V  C  L     360

TTTAACCTGCCGGAAGTCAGGGAGTCTTTCGGGGGCCAGAAGTGTGGGAACAGATTTGTG  1140
F  N  L  P  E  V  R  E  S  F  G  G  Q  K  C  G  N  R  F  V     380

GAAGAAGGAGAGGAGTGTGACTGTGGGGAGCCAGAGGAATGTATGAATCGCTGCTGCAAT  1200
E  E  G  E  E  C  D  C  G  E  P  E  E  C  M  N  R  C  C  N     400

GCCACCACCTGTACCCTGAAGCCGGACGCTGTGTGCGCACATGGGCTGTGCTGTGAAGAC  1260
A  T  T  C  T  L  K  P  D  A  V  C  A  H  G  L  C  C  E  D     420
```


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FIG. 15d

```
TGCCAGCTGAAGCCTGCAGGAACAGCGTGCAGGGACTCCAGCAACTCCTGTGACCTCCCA   1320
C  Q  L  K  P  A  G  T  A  C  R  D  S  S  N  S  C  D  L  P      440

GAGTTCTGCACAGGGGCCAGCCCTCACTGCCCAGCCAACGTGTACCTGCACGATGGGCAC   1380
E  F  C  T  G  A  S  P  H  C  P  A  N  V  Y  L  H  D  G  H      460

TCATGTCAGGATGTGGACGGCTACTGCTACAATGGCATCTGCCAGACTCACGAGCAGCAG   1440
S  C  Q  D  V  D  G  Y  C  Y  N  G  I  C  Q  T  H  E  Q  Q      480

TGTGTCACGCTCTGGGGACCAGGTGCTAAACCTGCCCCTGGGATCTGCTTTGAGAGAGTC   1500
C  V  T  L  W  G  P  G  A  K  P  A  P  G  I  C  F  E  R  V      500

AATTCTGCAGGTGATCCTTATGGCAACTGTGGCAAAGTCTCGAAGAGTTCCTTTGCCAAA   1560
N  S  A  G  D  P  Y  G  N  C  G  K  V  S  K  S  S  F  A  K      520

TGCGAGATGAGAGATGCTAAATGTGGAAAAATCCAGTGTCAAGGAGGTGCCAGCCGGCCA   1620
C  E  M  R  D  A  K  C  G  K  I  Q  C  Q  G  G  A  S  R  P      540

GTCATTGGTACCAATGCCGTTTCCATAGAAACAAACATCCCCCTGCAGCAAGGAGGCCGG   1680
V  I  G  T  N  A  V  S  I  E  T  N  I  P  L  Q  Q  G  G  R      560
```


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FIG. 15e

```
ATTCTGTGCCGGGGGACCCACGTGTACTTGGGCGATGACATGCCGGACCCAGGGCTTGTG   1740
I  L  C  R  G  T  H  V  Y  L  G  D  D  M  P  D  P  G  L  V      580

CTTGCAGGCACAAAGTGTGCAGATGGAAAAATCTGCCTGAATCGTCAATGTCAAAATATT   1800
L  A  G  T  K  C  A  D  G  K  I  C  L  N  R  Q  C  Q  N  I      600

AGTGTCTTTGGGGTTCACGAGTGTGCAATGCAGTGCCACGGCAGAGGGGTGTGCAACAAC   1860
S  V  F  G  V  H  E  C  A  M  Q  C  H  G  R  G  V  C  N  N      620

AGGAAGAACTGCCACTGCGAGGCCCACTGGGCACCTCCCTTCTGTGACAAGTTTGGCTTT   1920
R  K  N  C  H  C  E  A  H  W  A  P  P  F  C  D  K  F  G  F      640

GGAGGAAGCACAGACAGCGGCCCCATCCGGCAAGCAGAAGCAAGGCAGGAAGCTGCAGAG   1980
G  G  S  T  D  S  G  P  I  R  Q  A  E  A  R  Q  E  A  A  E      660

TCCAACAGGGAGCGCGGCCAGGGCCAGGAGCCCGTGGGATCGCAGGAGCATGCGTCTACT   2040
S  N  R  E  R  G  Q  G  Q  E  P  V  G  S  Q  E  H  A  S  T      680

GCCTCACTGACACTCATCTGAGCCCTCCCATGACATGGAGACCGTGACCAGTGCTGCTGC   2100
A  S  L  T  L  I  *                                             686
```


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FIG. 15f

```
AGAGGAGGTCACGCGTCCCCAAGGCCTCCTGTGACTGGCAGCATTGACTCTGTGGCTTTG   2160
CCATCGTTTCCATGACAACAGACACAACACAGTTCTCGGGGCTCAGGAGGGGAAGTCCAG   2220
CCTACCAGGCACGTCTGCAGAAACAGTGCAAGGAAGGGCAGCGACTTCCTGGTTGAGCTT   2280
CTGCTAAAACATGGACATGCTTCAGTGCTGCTCCTGAGAGAGTAGCAGGTTACCACTCTG   2340
GCAGGCCCCAGCCCTGCAGCAAGGAGGAAGAGGACTCAAAAGTCTGGCCTTTCACTGAGC   2400
CCCCACAGCAGTGGGGGAGAAGCAAGGGTTGGGCCCAGTGTCCCCTTTCCCCAGTGACAC   2460
CTCAGCCTTGGCAGCCCTGATGACTGGTCTCTGGCTGCAACTTAATGCTCTGATATGGCT   2520
TTTAGCATTTATTATATGAAAATAGCAGGGTTTTAGTTTTTAATTTATCAGAGACCCTGC   2580
CACCCATTCCATCTCCATCCAAGCAAACTGAATGGCATTGAAACAAACTGGAGAAGAAGG   2640
TAGGAGAAAGGGCGGTGAACTCTGGCTCTTTGCTGTGGACATGCGTGACCAGCAGTACTC   2700
AGGTTTGAGGGTTTGCAGAAAGCCAGGGAACCCACAGAGTCACCAACCCTTCATTTAACA   2760
AGTAAGAATGTTAAAAAGTGAAAACAATGTAAGAGCCTAACTCCATCCCCCGTGGCCATT   2820
ACTGCATAAAATAGAGTGCATCCCGCCC  2848
```


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FIG. 16

```
GGG GAA GAG TGT GAT TGT GGA GAA GAA GAG GAA TGT AAC AAC CCC TGC TGC AAT GCC TCT    60
G  E  E  C  D  C  G  E  E  E  E  C  N  N  P  C  C  N  A  S                       20

AAT TGT ACC CTG AGG CCG GGG GCG GAG TGT GCT CAC GGC TCC TGC TGC CAC CAG TGT AAG   120
N  C  T  L  R  P  G  A  E  C  A  H  G  S  C  C  H  Q  C  K                       40

CTG TTG GCT CCT GGG ACC CTG TGC CGC GAG CAG GCC AGG CAG TGT GAC CTC CCG GAG TTC   180
L  L  A  P  G  T  L  C  R  E  Q  A  R  Q  C  D  L  P  E  F                       60

TGT ACG GGC AAG TCT CCC CAC TGC CCT ACC AAC TTC TAC CAG ATG GAT GGT ACC CCC TGT   240
C  T  G  K  S  P  H  C  P  T  N  F  Y  Q  M  D  G  T  P  C                       80

GAG GGC GGC CAG GCc TAC TGC TAC AAC GGC ATG TGC CTC ACC TAC CAG GAG CAG TGC CAG   300
E  G  G  Q  A  Y  C  Y  N  G  M  C  L  T  Y  Q  E  Q  C  Q                      100

CAG CTG TGG GGA CCC GGA GCC CGA CCT GCC CCT GAC CTC TGC TTC GAG AAg GTG AAT GTG   360
Q  L  W  G  P  G  A  R  P  A  P  D  L  C  F  E  K  V  N  V                      120

GCA GGA GAC ACC TTT GGA AAC TGT GGA AAG GAC A     394
A  G  D  T  F  G  N  C  G  K  D        131
```

FIG. 17a

```
CGGAGCTGCCACTGGGCACCCCTTTCCCAAAGTGTTCAATGGATGCAACAGGAGGGAGCT   60
 G  A  A  T  G  H  P  F  P  K  V  F  N  G  C  N  R  R  E  L    20

GGACAGGTATCTGCAGTCAGGTGGTGGAATGTGTCTCTCCAACATGCCAGACACCAGGAT  120
 D  R  Y  L  Q  S  G  G  G  M  C  L  S  N  M  P  D  T  R  M    40

GTTGTATGGAGGCCGGAGGTGTGGGAACGGGTATCTGGAAGATGGGGAAGAGTGTGACTG  180
 L  Y  G  G  R  R  C  G  N  G  Y  L  E  D  G  E  E  C  D  C    60

TGGAGAAGAAGAGGAATGTAACAACCCCTGCTGCAATGCCTCTAATTGTACCCTGAGGCC  240
 G  E  E  E  E  C  N  N  P  C  C  N  A  S  N  C  T  L  R  P    80

GGGGGCGGAGTGTGCTCACGGCTCCTGCTGCCACCAGTGTAAGCTGTTGGCTCCTGGGAC  300
 G  A  E  C  A  H  G  S  C  C  H  Q  C  K  L  L  A  P  G  T   100

CCTGTGCCGCGAGCAGGCCAGGCAGTGTGACCTCCCGGAGTTCTGTACGGGCAAGTCTCC  360
 L  C  R  E  Q  A  R  Q  C  D  L  P  E  F  C  T  G  K  S  P   120

CCACTGCCCTACCAACTTCTACCAGATGGATGGTACCCCCTGTGAGGGCGGCCAGGCCTA  420
 H  C  P  T  N  F  Y  Q  M  D  G  T  P  C  E  G  G  Q  A  Y   140
```


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FIG. 17b

```
CTGCTACAACGGCATGTGCCTCACCTACCAGGAGCAGTGCCAGCAGCTGTGGGGACCCGG   480
 C  Y  N  G  M  C  L  T  Y  Q  E  Q  C  Q  Q  L  W  G  P  G     160

AGCCCGACCTGCCCCTGACCTCTGCTTCGAGAAGGTGAATGTGGCAGGAGACACCTTTGG   540
 A  R  P  A  P  D  L  C  F  E  K  V  N  V  A  G  D  T  F  G     180

AAACTGTGGAAAGGACATGAATGGTGAACACAGGAAGTGCAACATGAGAGATGCGAAGTG   600
 N  C  G  K  D  M  N  G  E  H  R  K  C  N  M  R  D  A  K  C     200

TGGGAAGATCCAGTGTCAGAGCTCTGAGGCCCGGCCCCTGGAGTCCAACGCGGTGCCCAT   660
 G  K  I  Q  C  Q  S  S  E  A  R  P  L  E  S  N  A  V  P  I     220

TGACACCACTATCATCATGAATGGGAGGCAGATCCAGTGCCGGGGCACCCACGTCTACCG   720
 D  T  T  I  I  M  N  G  R  Q  I  Q  C  R  G  T  H  V  Y  R     240

AGGTCCTGAGGAGGAGGGTGACATGCTGGACCCAGGGCTGGTGATGACTGGAACCAAGTG   780
 G  P  E  E  E  G  D  M  L  D  P  G  L  V  M  T  G  T  K  C     260

TGGCTACAACCATATTTGCCTTGAGGGGCAGTGCAGGAACACCTCCTTCTTTGAAACTGA   840
 G  Y  N  H  I  C  L  E  G  Q  C  R  N  T  S  F  F  E  T  E     280
```

FIG. 17c

```
AGGCTGTGGGAAGAAGTGCAATGGCCATGGGGTCTGTAACAACAACCAGAACTGCCACTG   900
 G  C  G  K  K  C  N  G  H  G  V  C  N  N  N  Q  N  C  H  C    300

CCTGCCGGGCTGGGCCCCGCCCTTCTGCAACACACCGGGCCACGGGGGCAGTATCGACAG   960
 L  P  G  W  A  P  P  F  C  N  T  P  G  H  G  G  S  I  D  S    320

TGGGCCTATGCCCCCTGAGAGTGTGGGTCCTGTGGTAGCTGGAGTGTTGGTGGCCATCTT  1020
 G  P  M  P  P  E  S  V  G  P  V  V  A  G  V  L  V  A  I  L    340

GGTGCTGGCGGTCCTCATGCTGATGTACTACTGCTGCAGACAGAACAACAAACTAGGCCA  1080
 V  L  A  V  L  M  L  M  Y  Y  C  C  R  Q  N  N  K  L  G  Q    360

ACTCAAGCCCTCAGCTCTCCCTTCCAAGCTGAGGCAACAGTTCAGTTGTCCCTTCAGGGT  1140
 L  K  P  S  A  L  P  S  K  L  R  Q  Q  F  S  C  P  F  R  V    380

TTCTCAGAACAGCGGGACTGGTCATGCCAACCCAACTTTCAAG                    1183
 S  Q  N  S  G  T  G  H  A  N  P  T  F  K                      394
```


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FIG. 18a Peptides used for the preparation of monoclonal antibody

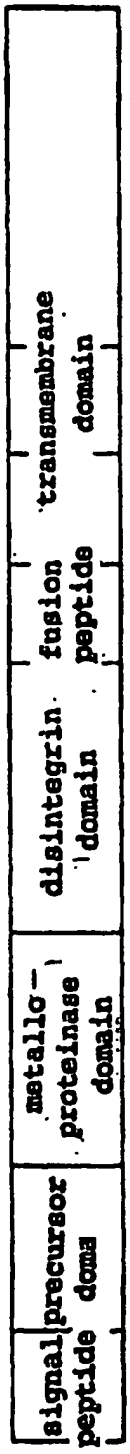

FIG. 18b Peptide sequences used for the preparation of monoclonal antibody

No.	Name	Sequence (N-terminal, C-terminal)
1	Pro-A	TTDSYKLVPAESMTNIC
2	MP-A	ADNREFQRQGKDLEKVKC
3	MP-B	FTRLHEFLDWRKIKC
4	DC-A	QLKPPGTACRGSSNSC
5	DC-B	GTACRGSSNSCDLPEFC
6	DC-C	GKDSKSAFAKCELRDAKC
7	DC-D	QGGASRPVIGTNAVSIETNIC
8	DE-A	LFNLPEVKQAFGGRKC

FIG. 19 Western blotting with anti-Meltrin monoclonal antibodies

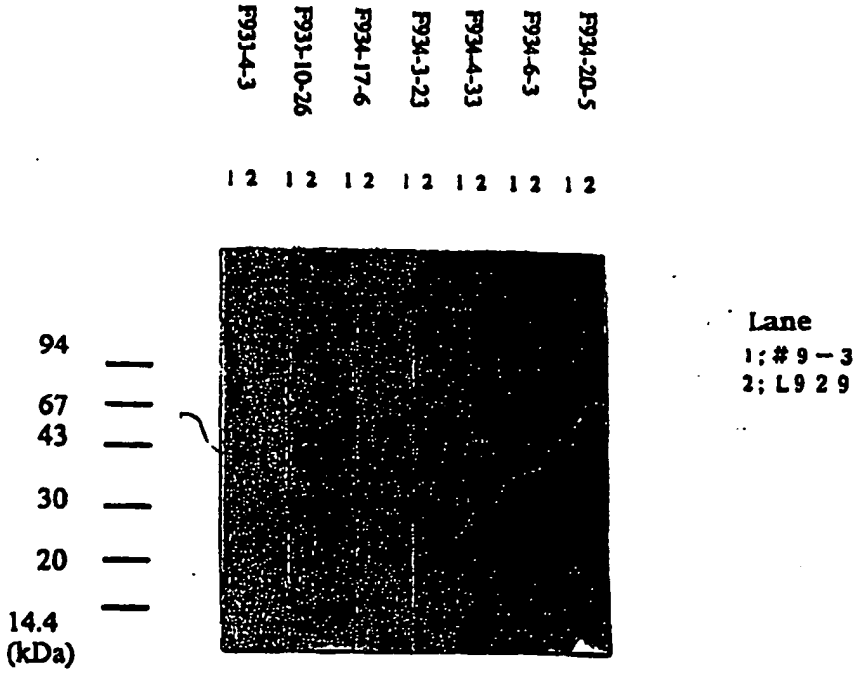

FIG. 20 Effects of anti-mouse Meltrin antibodies on the formation of myotube by C2 cells

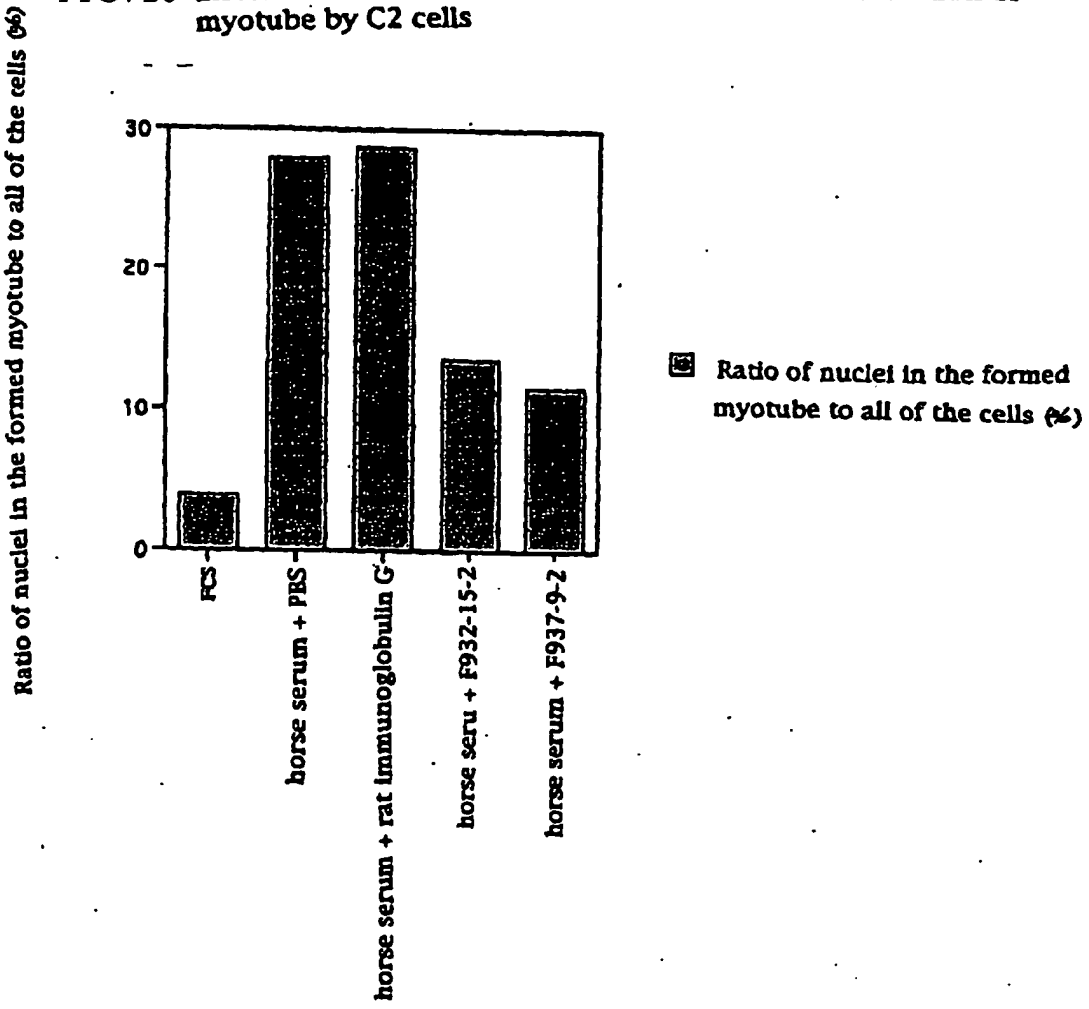

FIG. 21 Effects of anti-mouse Meltrin antibodies on the formation of pit (bone-resorption area) in mouse unfractionated bone cells

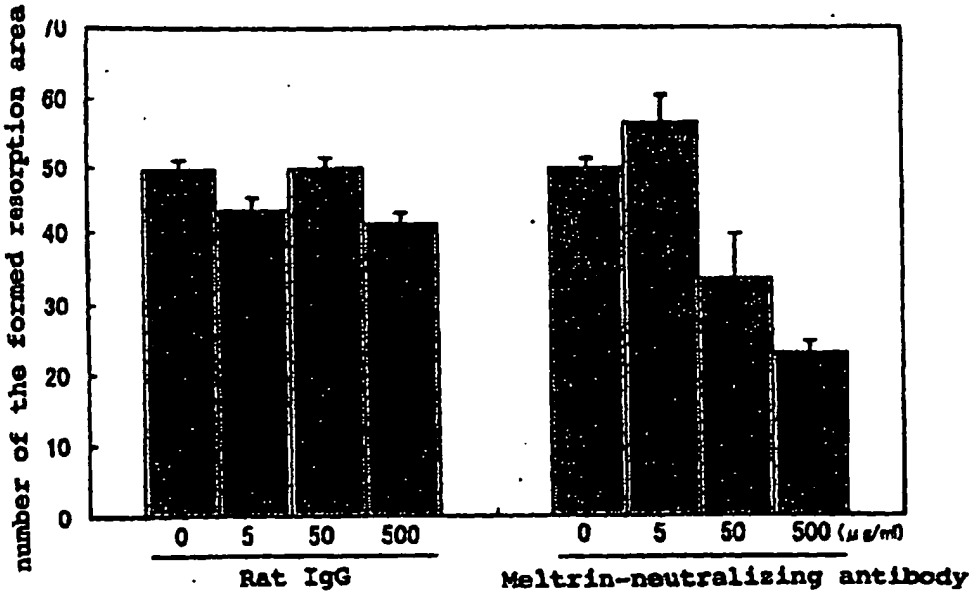

FIG. 22 Effects of anti-mouse Meltrin antibodies on the serum Ca values of the mouse fed with low Ca-content feed

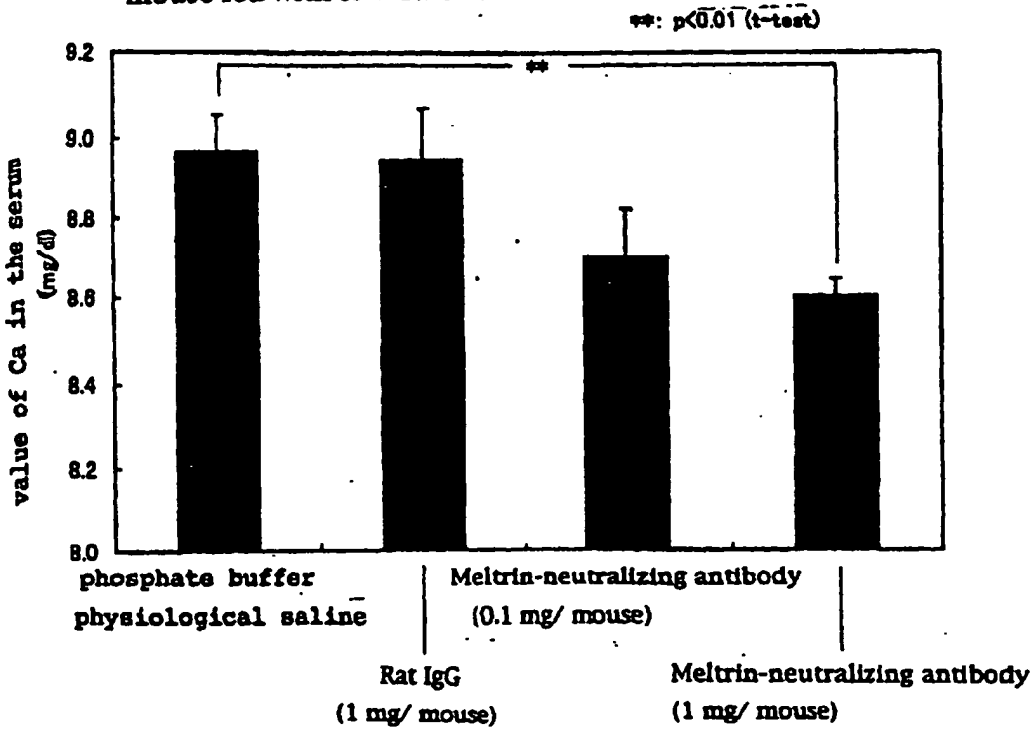

FIG. 23a

```
GCACAAAGTGTGCAGATGGAAAAATCTGCCTGAATCGTCAATGTCAAAATATTAGTGTCT  60
  T  K  C  A  D  G  K  I  C  L  N  R  Q  C  Q  N  I  S  V  F  20

TTGGGGTTCACGAGTGTGCAATGCAGTGCCACGGCAGAGGGGTGTGCAACAACAGGAAGA 120
  G  V  H  E  C  A  M  Q  C  H  G  R  G  V  C  N  N  R  K  N  40

ACTGCCACTGCGAGGCCCACTGGGCACCTCCCTTCTGTGACAAGTTTGGCTTTGGAGGAA 180
  C  H  C  E  A  H  W  A  P  P  F  C  D  K  F  G  F  G  G  S  60

GCACAGACAGCGGCCCCATCCGGCAAGCAGATAACCAAGGTTTAACCATAGGAATTCTGG 240
  T  D  S  G  P  I  R  Q  A  D  N  Q  G  L  T  I  G  I  L  V  80

TGACCATCCTGTGTCTTCTTGCTGCCGGATTTGTGGTTTATCTCAAAAGGAAGACCTTGA 300
  T  I  L  C  L  L  A  A  G  F  V  V  Y  L  K  R  K  T  L  I 100

TACGACTGCTGTTTACAAATAAGAAGACCACCATTGAAAAACTAAGGTGTGTGCGCCCTT 360
  R  L  L  F  T  N  K  K  T  T  I  E  K  L  R  C  V  R  P  S 120

CCCGGCCACCCCGTGGCTTCCAACCCTGTCAGGCTCACCTCGGCCACCTTGGAAAAGGCC 420
  R  P  P  R  G  F  Q  P  C  Q  A  H  L  G  H  L  G  K  G  L 140
```


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FIG. 23b

```
TGATGAGGAAGCCGCCAGATTCCTACCCACCGAAGGACAATCCCAGGAGATTGCTGCAGT  480
  M  R  K  P  P  D  S  Y  P  P  K  D  N  P  R  R  L  L  Q  C   160

GTCAGAATGTTGACATCAGCAGACCCCTCAACGGCCTGAATGTCCCTCAGCCCCAGTCAA  540
  Q  N  V  D  I  S  R  P  L  N  G  L  N  V  P  Q  P  Q  S  T   180

CTCAGCGAGTGCTTCCTCCCCTCCACCGGGCTCCACGTGCACCTAGCGTCCCTGCCAGAC  600
  Q  R  V  L  P  P  L  H  R  A  P  R  A  P  S  V  P  A  R  P   200

CCCTGCCAGCCAAGCCTGCACTTA  624
  L  P  A  K  P  A  L     207
```


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FIG. 24a

```
CGGAGCTGCCACTGGGCACCCCTTTCCCAAAGTGTTCAATGGATGCAACAGGAGGGAGCT    60
 G  A  A  T  G  H  P  F  P  K  V  F  N  G  C  N  R  R  E  L     20

GGACAGGTATCTGCAGTCAGGTGGTGGAATGTGTCTCTCCAACATGCCAGACACCAGGAT   120
 D  R  Y  L  Q  S  G  G  G  M  C  L  S  N  M  P  D  T  R  M     40

GTTGTATGGAGGCCGGAGGTGTGGGAACGGGTATCTGGAAGATGGGGAAGAGTGTGACTG   180
 L  Y  G  G  R  R  C  G  N  G  Y  L  E  D  G  E  E  C  D  C     60

TGGAGAAGAAGAGGAATGTAACAACCCCTGCTGCAATGCCTCTAATTGTACCCTGAGGCC   240
 G  E  E  E  E  C  N  N  P  C  C  N  A  S  N  C  T  L  R  P     80

GGGGGCGGAGTGTGCTCACGGCTCCTGCTGCCACCAGTGTAAGCTGTTGGCTCCTGGGAC   300
 G  A  E  C  A  H  G  S  C  C  H  Q  C  K  L  L  A  P  G  T    100

CCTGTGCCGCGAGCAGGCCAGGCAGTGTGACCTCCCGGAGTTCTGTACGGGCAAGTCTCC   360
 L  C  R  E  Q  A  R  Q  C  D  L  P  E  F  C  T  G  K  S  P    120

CCACTGCCCTACCAACTTCTACCAGATGGATGGTACCCCCTGTGAGGGCGGCCAGGCCTA   420
 H  C  P  T  N  F  Y  Q  M  D  G  T  P  C  E  G  G  Q  A  Y    140
```


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FIG. 24b

```
CTGCTACAACGGCATGTGCCTCACCTACCAGGAGCAGTGCCAGCAGCTGTGGGGACCCGG   480
 C  Y  N  G  M  C  L  T  Y  Q  E  Q  C  Q  Q  L  W  G  P  G     160

AGCCCGACCTGCCCCTGACCTCTGCTTCGAGAAGGTGAATGTGGCAGGAGACACCTTTGG   540
 A  R  P  A  P  D  L  C  F  E  K  V  N  V  A  G  D  T  F  G     180

AAACTGTGGAAAGGACATGAATGGTGAACACAGGAAGTGCAACATGAGAGATGCGAAGTG   600
 N  C  G  K  D  M  N  G  E  H  R  K  C  N  M  R  D  A  K  C     200

TGGGAAGATCCAGTGTCAGAGCTCTGAGGCCCGGCCCCTGGAGTCCAACGCGGTGCCCAT   660
 G  K  I  Q  C  Q  S  S  E  A  R  P  L  E  S  N  A  V  P  I     220

TGACACCACTATCATCATGAATGGGAGGCAGATCCAGTGCCGGGGCACCCACGTCTACCG   720
 D  T  T  I  I  M  N  G  R  Q  I  Q  C  R  G  T  H  V  Y  R     240

AGGTCCTGAGGAGGAGGGTGACATGCTGGACCCAGGGCTGGTGATGACTGGAACCAAGTG   780
 G  P  E  E  E  G  D  M  L  D  P  G  L  V  M  T  G  T  K  C     260

TGGCTACAACCATATTTGCCTTGAGGGGCAGTGCAGGAACACCTCCTTCTTTGAAACTGA   840
 G  Y  N  H  I  C  L  E  G  Q  C  R  N  T  S  F  F  E  T  E     280
```


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FIG. 24c

```
AGGCTGTGGGAAGAAGTGCAATGGCCATGGGGTCTGTAACAACAACCAGAACTGCCACTG   900
 G  C  G  K  K  C  N  G  H  G  V  C  N  N  N  Q  N  C  H  C    300

CCTGCCGGGCTGGGCCCCGCCCTTCTGCAACACACCGGGCCACGGGGGCAGTATCGACAG   960
 L  P  G  W  A  P  P  F  C  N  T  P  G  H  G  G  S  I  D  S    320

TGGGCCTATGCCCCCTGAGAGTGTGGGTCCTGTGGTAGCTGGAGTGTTGGTGGCCATCTT  1020
 G  P  M  P  P  E  S  V  G  P  V  V  A  G  V  L  V  A  I  L    340

GGTGCTGGCGGTCCTCATGCTGATGTACTACTGCTGCAGACAGAACAACAAACTAGGCCA  1080
 V  L  A  V  L  M  L  M  Y  Y  C  C  R  Q  N  N  K  L  G  Q    360

ACTCAAGCCCTCAGCTCTCCCTTCCAAGCTGAGGCAACAGTTCAGTTGTCCCTTCAGGGT  1140
 L  K  P  S  A  L  P  S  K  L  R  Q  Q  F  S  C  P  F  R  V    380

TTCTCAGAACAGCGGGACTGGTCATGCCAACCCAACTTTCAAGCCGGAATTCCGGGCCCC  1200
 S  Q  N  S  G  T  G  H  A  N  P  T  F  K  P  E  F  R  A  P    400

CCACAGCCCACACCACCATGACAAGGGCCACCAATTCCACGGCCACACCCTCCTCCACTC  1260
 H  S  P  H  H  H  D  K  G  H  Q  F  H  G  H  T  L  L  H  S    420
```


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FIG. 24d

```
TGGGGACGACCCGGATCCTCACTGAGCTGACCACAACAGCCACTACAACTGCAGCCACTG   1320
 G  D  D  P  D  P  H  *                                          427

GATCCACGGCCACCCTGTCCTCCACCCCAGGGACCACCTGGATCCTCACAGAGCCGAGCA   1380
CTATAGCCACCGTGATGGTGCCCACCGGTTCCACGGCCACCGCCTCCTCCACTCTGGGAA   1440
CAGCTCACACCCCCAAAGTGGTGACCACCATGGCCACTATGCCCACAGCCACTGCCTCCA   1500
CGGTTCCCAGCTCGTCCACCGTGGGGACCACCCGCACCCCTGCAGTGCTCCCCAGCAGCC   1560
TGCCAACCTTCAGCGTGTCCACTGTGTCCTCCTCAGTCCTCACCACCCTGAGACCCACTG   1620
GCTTCCCCAGCTCCCACTTCTCTACTCCCTGCTTCTGCAGGGCATTTGGACAGTTTTTCT   1680
CGCCCGGGGAAGTCATCTACAATAAGACCGACCGAGCCGGCTGCCATTTCTACGCAGTGT   1740
GCAATCAGCACTGTGACATTGACCGCTTCCAGGGCGCCTGTCCCACCTCCCCACCGCCAG   1800
TGTCCTCCGCCCCGCTGTCCTCGCCCTCCCCTGCCCCTGGCTGTGACAATGCCATCCCTC   1860
TCCGGCAGGTGAATGAGACCTGGACCCTGGAGAACTGCACGGTGGCCAGGTGCGTGGGTG   1920
ACAACCGTGTCGTCCTGCTGGACCCAAAGCCTGTGGCCAACGTCACCTGCGTGAACAAGC   1980
ACCTGCCCATCAAAGTGTCGGACCCGAGCCAGCCCTGTGACTTCCACTATGAGTGCGAGT   2040
GCATCTGCAGCATGTGGGGCGGCTCCCACTATTCCACCTTTGACGGCACCTCTTACACCT   2100
TCCGGGGCAACTGCACCTATGTCCTCATGAGAGAGATCCATGCACGCTTTGGGAATCTCA   2160
GCCTCTACCTGGACAACCACTACTGCACGGCCTCTGCCACTGCCGCTGCCGCCCGCTGCC   2220
CCCGCGCCCTCAGCATCCACTACAAGTCCATGGATATCGTCCTCACTGTCACCATGGTGC   2280
ATGGGAAGGAGGAGGGCCTGATCCTGTTTGACCAAATTCCGGTGAGCAGCGGTTTCAGCA   2340
```


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FIG. 24e

```
AGAACGGCGTGCTTGTGTCTGTGCTGGGGACCACCACCATGCGTGTGGACATTCCTGCCC   2400
TGGGCGTGAGCGTCACCTTCAATGGCCAAGTCTTCCAGGCCCGGCTGCCCTACAGCCTCT   2460
TCCACAACAACACCGAGGGCCAGTGCGGCACCTGCACCAACAACCAGAGGGACGACTGTC   2520
TCCAGCGGGACGGAACCACTGCCGCCAGTTGCAAGGACATGGCCAAGACGTGGCTGGTCC   2580
CCGACAGCAGAAAGGATGGCTGCTGGGCCCCGACTGGCACACCCCCCACTGCCAGCCCCG   2640
CAGCCCCGGTGTCTAGCACACCCACCCCG  2669
```


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